Drug use in pregnancy

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Exploring the field of Disease Modifying Antirheumatic Drugs in pregnancy

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RIJKSUNIVERSITEIT GRONINGEN

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General introduction

Recently it was confirmed that about two-third of the Dutch population suffering from a rheumatic disease are younger then 65 years of age. Even more important, about 10% of them are of childbearing age (20-39 years).[1] Especially at young age early and effective treatment of a rheumatic disease is of great necessity.[2] During the past decades several new disease modifying anti-rheumatic drugs (DMARDs) have been developed.

Before new drugs are approved to the market animal testing should illustrate effectiveness and safety as well as possible teratogenic and embryo toxic properties. However, results from animal testing do not always predict the teratogenic effects of drugs in humans. This became very clear after the thalidomide disaster in the last century. Routine screening in rodents did not show any teratogenic effects of thalidomide and therefore it was thought to be safe. Thalidomide was used in the treatment of different disorders such as anxiety, insomnia, gastritis and tension; it was furthermore promoted as a safe anti-emetic drug during pregnancy.[3] The drug was withdrawn from the market a few years after its introduction due to severe teratogenic effects causing limb defects, ear malformations and/or hearing loss, ocular anomalies and various other anomalies.[3] The use of thalidomide showed us that although the drug was thought to be safe from animal studies, it was clearly not safe in humans. The thalidomide disaster demonstrated the importance of pharmacovigilance and in particular of research on drug use in relation to birth defects in humans.

Pregnancy, drug use and risks: issues encountered

Before risks associated with drug use during pregnancy can be identified, drug utilization studies should be performed to identify the magnitude of the problem. Drug utilizations studies showed that drug use during pregnancy varies, estimations range from 44 to 99%.[4-6] Variation in these estimations occurs due to the inclusion or exclusion of for example folic acid and the use of over-the-counter (OTC) drugs as well as data sources used. Drugs for chronic conditions and occasional or incidental use are prescribed less during pregnancy in contrast to drugs which are regularly used during pregnancy such as folic acid, anti-emetic

drugs and antacids.[4] For identification of drugs prescribed during pregnancy several national and international databases are available. The Groningen Interaction Database (IADB.nl) contains pharmacy dispensing data [7]; prescribed drugs dispend during a certain period can be identified and in this way the expected exposure (when the patient is adherent to her therapy) can be determined. The general practice research database (GPRD, UK)[8] is also able to identify possible exposure; data are collected at the general practitioner including date and name of drugs prescribed. Claim or health insurance databases are used as well in an attempt to identify drug exposure.[5;6;9;10] Nevertheless, these databases are only able to identify possible exposure; none of these databases can determine the actual use of the drug. Interviews with patients or questionnaires can be useful to determine whether drugs are actually being used during pregnancy.[11;12] However, this type of data collection may introduce recall bias due to time between use of the drug and the interview or questionnaire.

Approximately 65% of all congenital malformations are of unknown origin; 20-25% of all congenital malformations are explained by genetic defects and environmental factors. From the latter chemicals and drugs account for only 8-11% [13] of all birth defects. Congenital malformations can be divided into major and minor malformations, the risk of major congenital malformation among the general population is estimated between 1 and 3%.[13]
In principle drugs could be classified in high-risk teratogens such as thalidomide and isotretinoin, moderate-risk teratogens and low-risk teratogens. It is believed that moderate-risk teratogens cause an increase of a specific birth defect by a factor somewhere between 2 and 10 compared to the baseline risk for that specific birth defect [12].
To identify teratogens in the post-marketing setting two main study designs have been developed; follow-up studies and case-control surveillances. Follow-up studies are able to identify women exposed to a certain drug; high-risk teratogens can be identified efficiently and small numbers suffice. However, in follow-up studies relatively small samples are recruited and they lack statistical power, therefore they are insufficient to identify moderate- and low-risk teratogens. Case-

control studies have more substantial statistical power and are therefore more appropriate to identify moderate- or low-risk teratogens.[12]

Rheumatic diseases, pharmacotherapy and pregnancy: changing policies

Pregnancy in rheumatic diseases

In the past women with a rheumatic disease were told not to have children for several reasons related to their chronic disease. The treatment of rheumatic diseases focused on symptom control with non-steroidal anti-inflammatory drugs (NSAIDs) to achieve pain relief and decrease of the swelling. [14;15] It was thought that the damage caused to the joints leads to inability of the women to take care of a child. Insight on the course of the disease during pregnancy and changes in the pharmacotherapy changed this perspective. It is believed that RA does not comprise fetal outcome and approximately 75% of the RA patients experience an improvement of their symptoms during pregnancy.[16] In about 65% of the pregnancies remission of RA is described and drugs can be stopped.[16] In contrast, women with systemic lupus erythematosus (SLE) often have symptoms during pregnancy followed by an active disease after delivery, therefore the disease should be well controlled with drugs. In women with SLE fetal outcome can be affected, adverse outcomes such as fetal death, preterm birth and intrauterine growth retardation are seen.[16] In many other rheumatic diseases such as ankylosing spondylitis (Bechterew disease), Behçet's disease and juvenile chronic arthritis fetal outcome does not seem to be affected.[16]

Pharmacotherapy in rheumatic disease

Disease modifying anti-rheumatic drugs (DMARDs) are the main drugs used in nowadays treatment of rheumatic diseases.[14;17-19] The treatment focuses on the prevention or control of joint damage as soon as a rheumatic disease is discovered. Guidelines state methotrexate to be the first choice DMARD, due to its effectiveness, safety and low costs. [14;17;18;20] If methotrexate single therapy fails, other DMARDs such as hydroxychloroquine, sulfasalazine or leflunomide can be added. A new group of DMARDs, the "biologicals", are recently introduced in the treatment of rheumatic diseases: namely the tumor necrosis factor alfa (TNFα)

blocking drugs etanercept, adalimumab and infliximab. They are prescribed to patients who do not respond to a combination of other DMARDs[20], although there is evidence that they are also effective in the first line treatment [21]. Other DMARDs traditionally being used in the treatment of rheumatic diseases are gold preparations (gold sodium thiomalate, aurothioglucose and an oral variant: auranofin), chloroquine and hydroxychloroquine (antimalarial drug), azathioprine and cyclosporine (immunosuppressive drugs), d-penicillamine and cyclophosphamide (alkylating agent)[16]. Newer biologicals recently admitted to the market for the treatment of rheumatic diseases are anakinra (interleukin-1 receptor antagonist), abatacept (anti-CTLA-4: costimulation blocker) and rituximab (chimeric anti-CD20 monoclonaal antibody).[15;18;20;22;23]

Pharmacotherapy in rheumatic diseases during pregnancy

Many of the DMARDs can not be used or should be used with caution during pregnancy. In order to guide health care providers in prescribing drugs to pregnant women several classification systems have been developed. The United States (FDA), Australia and Sweden all developed their own classification system [24-27]. Each drug can be classified according to these systems (see appendix 1) and although the systems may vary, general recommendations do apply for most drugs. Methotrexate and leflunomide are considered to be teratogenic and should therefore not be used before or during pregnancy. Drugs such as cyclosporin, cyclophosphamide, penicillamine, TNFα blocking drugs, anakinra, and rituximab should be avoided during pregnancy. Information for many of these drugs is scarce and recommendations lack animal or human data or are based on inadequate animal or human studies, case reports, or small exposed cohorts. [28;29] Hydroxychloroquine, chloroquine and azathioprine should also be avoided during pregnancy, although for these drugs therapy benefits may outweigh potentials risks for the fetus. This has to be judged individually in every single case. Sulfasalazine is the only drug that is safe according to the risk classification systems [24-27].

Pharmacotherapy in rheumatic diseases during pregnancy: the dilemmas

Patients with a rheumatic disease will have many questions about their disease and drug use in relation to pregnancy. 'Do I want to become pregnant with this disease, can my baby get the disease as well, does a pregnancy influence my disease, can I take drugs while I am pregnant and can I take care of my child with this disease?' are just a few of the dilemmas women have to deal with. Clinicians and their patients have to discuss their options, using guidelines, information leaflets and experience. However, in many cases the available information is limited and evidence and experience is scarce, leading to difficult choices for the clinician and their patients.

Nowadays the Internet is a widely used medium and the search for information might look easy. The Internet provides more than a million websites about 'rheumatoid arthritis' and 'systemic lupus erythematosus', and in relation to pregnancy about half a million websites are available. In addition, information can be obtained from books, leaflets, magazines, other patients, family and friends and health care professionals. National as well as international associations of rheumatism patients and rheumatism associations and organizations of professionals try to support patients with informative websites. They translate the scientific information and considerations into a compact and understandable text on the website or in leaflets.

Some of the information that can be found on the Internet will be misleading, incomplete or even untrue. For the patient it might be difficult to distinguish between information that is reliable and useful and information that is not. The bulk of information might lead to more questions rather then to answers. Questions which can be posed to health care professionals such as the rheumatologist or general practitioner but also Internet forums show wide ranges of questions asked and answers given. Topics on these forums vary from general questions about RA and pregnancy to very specific questions about continuation or discontinuation of drugs before and during pregnancy. Other patients respond by sharing their experiences and knowledge or refer to informative websites. It was seen that patients felt empowered by participation in online support groups [30]. The total

search for information hopefully leads to answers, although evidence on drug use during pregnancy is often scarce and women might be left with the questions.

Objectives of this thesis

In this thesis the following objectives are formulated and explored:

1. The current knowledge on DMARD use during pregnancy;
2. Drugs used in rheumatic diseases among pregnant women;
3. Risks associated with the use of DMARDs during pregnancy
4. The perspective of rheumatologists on the treatment of pregnant and non-pregnant female patients;
5. The way female patients handle questions and information about the use of their drugs and their disease around pregnancy.

Current knowledge from literature on DMARD use during pregnancy mainly focused on studies performed in patients with a rheumatic disease will be discussed in chapter 1.
The use of NSAIDs and acetylsalicylic acid (ASA) as well as a detailed description of the use of sulfasalazine, azathioprine and methotrexate before, during and after pregnancy in the Netherlands will be discussed in chapter 2 and 3.
Chapter 4 and 5 will describe the use of DMARDs in the United Kingdom and risks associated with the use of DMARDs in relation to gestational age and birth defects.
Chapter 6 will discuss the perspective of Dutch rheumatologists on the treatment of pregnant patients as well as non-pregnant patients.
Chapter 7 will discuss women's questions about a rheumatic disease, drugs and a (recent) pregnancy or a (past) desire to become pregnant.
At the end of this thesis the overall findings and conclusions of this thesis will be discussed and recommendation for future research will be made.

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Appendix 1

	FDA pregnancy risk category [25-27]
A	Controlled studies in women fail to demonstrate a risk to the fetus in the first trimester (and there is no evidence of a risk in later trimesters), and the possibility of fetal harm appears remote.
B	Either animal-reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women or animal-reproduction studies have shown adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of a risk in later trimesters).
C	Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.
D	There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).
X	Studies in animals or human beings have demonstrated fetal abnormalities or there is evidence of fetal risk based on human experience or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant.

	Australian pregnancy risk category [26;28]
A	Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed.
B1	Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage.
B2	Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.
B3	Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.
C	Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.
D	Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.
X	Drugs which have such a high risk of causing permanent damage to the fetus that they should not be used in pregnancy or when there is a possibility of pregnancy.

	Swedish pregnancy risk category [26;29]
A	Medicinal products which may be assumed to have been used by a large number of pregnant women and women of child-bearing age without any identified disturbance in the reproductive process, e.g. an increased incidence of malformations or other direct or indirect effects on the fetus. This category comprises: drugs that have been available for many years; those that have been used by many pregnant women and women of child-bearing age and; drugs for which satisfactory retrospective studies in pregnant women are considered to have been carried out.
B	Medicinal products which may be assumed to have been used only by a limited number of pregnant women and women of child-bearing age without any identified disturbance in the reproductive process having been noted so far, e.g. an increased incidence of malformations or other direct or indirect harmful effects on the fetus. As experience of effects of medicinal products in man is limited in this category, results of reproduction toxicity studies in animals are indicated by allocation to one of 3 subgroups B1, B2 or B3 according to the following definitions:
B1	Reproduction toxicity studies have not given evidence of an increased incidence of fetal damage or other deleterious effects on the reproductive process.
B2	Reproduction toxicity studies are inadequate or lacking, but available data do not indicate an increased incidence of fetal damage or other deleterious effects on the reproductive process.
B3	Reproduction toxicity studies in animals have revealed an increased incidence of fetal damage or other deleterious effects on the reproductive process, the significance of which is considered uncertain in humans.
C	Medicinal products, which by their pharmacological effects have caused, or must be suspected of causing, disturbances in the reproductive process that may involve risk to the fetus without being directly teratogenic. If experimental studies in animals have indicated an increased occurrence of fetal injuries or other disturbances of the reproductive process of uncertain insignificance in humans, these findings are to be stated for drugs in this category.
D	Medicinal products which have caused an increased incidence of fetal malformations or other permanent damage in humans, or which, on the basis of e.g. reproduction toxicity studies, must be suspected of doing so. This category comprises drugs with primary teratogenic effects that may directly or indirectly have a harmful effect on the fetus.

Chapter 1

Disease Modifying Anti-Rheumatic Drugs in pregnancy; a review and implications for the future

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Abstract

Introduction: Drug use during pregnancy is sometimes unavoidable especially in chronic inflammatory diseases such as rheumatoid arthritis (RA). The use of Disease Modifying Anti-Rheumatic Drugs (DMARD) already often starts in the early stage of RA; therefore women of reproductive age are at risk for exposure to a DMARD at time of conception as well as during pregnancy. The aim of this study was to review recent literature about DMARD used for rheumatic diseases in pregnancy and to describe the type of study designs and results reported.

Method: The English medical and pharmacological literature was searched by using generic as well as the brand name of all DMARD. Several keywords related to pregnancy were used to refine the search and we focused our search on human and original data, monotherapy and rheumatic diseases.

Results: Our search revealed only 29 studies; eight on hydroxychloroquine/chloroquine, 13 on methotrexate, three on sulfasalazine, and six on azathioprine. With respect to hydroxychloroquine, most studies concluded that it could be safely used in systemic lupus erythematosus or RA. The same conclusions can be drawn from the azathioprine studies, but the available evidence is scarce. Although the evidence regarding the safety of methotrexate during pregnancy is conflicting, a high rate of pregnancy losses indicates a risk to the fetus. For each individual case it must be decided whether the benefits may outweigh the potential risks. No major teratogenic effects of sulfasalazine are seen although teratogenic effects still can not be excluded. For all other DMARD, the information on their use in pregnancy was limited. When identifying teratogens two study designs are recommended: case-control surveillances or follow-up studies. Among the 29 studies found only two case-control studies and one large cohort was identified.

Conclusions: This review underscores the gross absence of data on safety and risks of DMARD use during conception and pregnancy. Despite limited information on the influence of DMARD in pregnant women with a rheumatic disease, these are drugs used in clinical practice and despite the advice to avoid pregnancy, patients become pregnant during the use of DMARD. Therefore we consider a monitoring system for DMARD use during pregnancy could be of great help to contribute to the research of teratogenity of DMARDs. In addition, this will improve the knowledge to provide more solid information to patients and health care professionals in RA treatment.

Introduction

A chronic disease requires continual attention of the patient and the attending physician. In case of a progressive chronic inflammatory disease such as rheumatoid arthritis (RA), continues medication treatment is often inevitably. Because of a change in the objective of pharmacotherapy, i.e. to include disease control as well as symptom control, treatment with disease modifying anti-rheumatic drugs (DMARDs) is commenced in the early stages of the rheumatic diseases.[1;2] Therefore, women who are at the reproductive age and who have RA are at risk for exposure to a DMARD or other anti-rheumatic drugs at the time of conception as well as during pregnancy. Although many women will experience a spontaneous remission of their disease during pregnancy, and therefore continuation of medication might not be necessary, the risk of drug exposure during conception, as well as in the first stage of the pregnancy remains.
For those, who do require medication during their pregnancy, clinical decisions considering the mother as well as the child have to be made with respect to pharmacotherapy. Ideally, these decisions will be based on evidence-based information. However, for obvious reasons, random control trials (RCTs) hardly ever include pregnant women. As a consequence, decisions in daily practice with respect to the use of DMARDs in pregnancy will be based on animal experiments, observation studies in humans, and expert opinion, rather than analytical epidemiological studies such as case-control surveillances or follow-up studies. Mitchell[5] recommended these kinds of studies as the best available evidence for identifying teratogens.
The aim of this study is to review the recent literature on the use of DMARDs in rheumatic diseases in pregnancy and describe the type of study designs employed and the results reported.

Methods

Medical and pharmacological literature in English was searched for original manuscripts published between 1990 and 2004 using EMBASE, Cochrane Library, and Medline. The generic (adalimumab, anakinra, auranofin, gold sodium thiomalate, aurothioglucose, azathioprine/6-mercaptopurine, (hydroxy)chloroquine,

cyclosporine, cyclophosphamide, etanercept, infliximab, leflunomide, methotrexate, penicillamine and sulfasalazine) or brand names of all DMARDs and biologicals were used at the start of the search and this search was refined with one of the following keywords or variations: ‘pregnant’, ‘pregnancy outcome’, ‘birth defects’, ‘malformations’, or ‘adverse outcome’. In addition, the reference lists of appropriate articles, related books, guidelines, and prescribing information were used.
Primarily, the search was restricted to human studies describing original data; reviews were thereby excluded. If no information could be found on human studies, results from animal studies were considered (briefly discussed in this review). The search was also restricted to the use of monotherapy in rheumatic diseases (i.e. RA and systemic lupus erythematosus (SLE)). Studies describing the use of anti-rheumatic drugs in other indications (e.g. azathioprine post-transplantation) were not included.
All eligible publications were systematically scored for information on specific study design (e.g. case report, cohort, or RCT) and outcome of the pregnancies, (e.g. number of live births, birth defects and miscarriage or abortion (table 3-6). Comments were noted regarding: birth defects; the indication for which the medication was taken; the follow-up time after pregnancy; the use of co-medication; the exposure time or period of the drug; and miscellaneous findings. If there was no information available on the specific item it will be mentioned as: no information.

Results

General issues

Table 1 shows all DMARDs including the FDA pregnancy risk category (definitions in table 2), indications and dose regimens of the drugs. Currently, 16 drugs (including 4 biologicals) are approved for disease modification of RA. In addition to their beneficial effect on the course of RA, the majority are also labeled for other indications .The dose regimen varies between DMARDs and also per indication; the dose in RA treatment is shown in table 1.
According to the FDA classification, leflunomide and methotrexate (pregnancy-risk category X) should not be used in pregnancy. Cyclophosphamide, azathioprine

and penicillamine are in pregnancy-risk category D, meaning that their use during pregnancy may outweigh the potential teratogenic risks. Most drugs are categorized C or B (table 2), indicating that adequate and well-controlled studies in pregnant women have either not been performed or showed no risk. No drug is in pregnancy risk category A. Adaliumab is the only agent which has not yet been assigned a pregnancy-risk category. Thirty studies were identified in the search: hydroxychloroquine/chloroquine (eight studies); methotrexate (13); sulfasalazine (3); azathioprine (6). Detailed information on the individual studies can be found in table II-V. Hereafter, other DMARDs are only briefly discussed in this article, because of lack of information.

Table 1. Pregnancy risk categories according to the US FDA[6]

Category	Criteria
A	Adequate, well-controlled studies in pregnant women have not shown an increased risk of fetal abnormalities.
B	Animal studies have revealed no evidence of harm to the fetus; however, there are no adequate and well-controlled studies in pregnant women OR animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus.
C	Animal studies have shown an adverse effect, and there are no adequate and well-controlled studies in pregnant women OR no animal studies have been conducted, and there are no adequate and well-controlled studies in pregnant women.
D	Studies, adequate well-controlled or observational, in pregnant women have demonstrated a risk to the fetus. However, the benefits of therapy may outweigh the potential risk.
X	Studies, adequate well-controlled or observational, in animals or pregnant women have demonstrated positive evidence of fetal abnormalities. The use of the product is contraindicated in women who are or may become pregnant.

Table 2. Disease modifying anti-rheumatic drugs, their indications, FDA pregnancy-risk category, and dose regimen for rheumatoid arthritis (RA)[4,5]

Drug	Risk category*	Indications[a]	Dosage[a]
Adalimumab	-	RA	40 mg weekly sc
Anakinra	B	RA	100 mg daily sc
Auranofin	C	RA	3 mg twice daily
Gold sodium thiomalate	C	RA	50 mg weekly im (for 20 weeks)
Aurothioglucose	C	RA, JIA, psoriatic arthritis	50 mg weekly im
Azathioprine	D	RA, CD, organ transplantation, chronic active hepatitis	1-2.5 mg/kg/day
Chloroquine	C	Malaria prophylaxis, liver amoebiasis, RA, SLE	150-300 mg/day (7-10 weeks), 100-200 mg (maintenance treatment)
Cyclosporin	C	Prophylaxis after organ transplantation, psoriasis, RA	2.5 mg/kg (2 doses/day) 3-4 mg/kg/day (maintenance treatment)
Cyclophos-phamide	D	Chronic lymphatic leukemia, auto-immune diseases such as SLE	50-200 mg/day orally
Etanercept	B	RA, polyarticular JIA, psoriatic arthritis	25 mg twice weekly
Hydroxy-chloroquine	C	Malaria prophylaxis, RA, SLE, DLE, photodermatoses	400 mg daily
Infliximab	C	CD, RA, AS	3 mg/kg iv
Leflunomide	X	RA	100 mg/day (3 days), 10-20 mg/day (maintenance treatment)
Methotrexate	X	Cancer, psoriasis, RA	7.5-10 mg/week or 2.5-5 mg thrice weekly
Penicillamine	D	RA, metal intoxication	150 mg/day (start)
Sulfasalazine	B	CU, CD, RA, PU	1000 mg twice daily, orally

* See table 1 for definitions

a AS= ankylosing spondylitis; CD=Crohn's Disease; DLE=Discoid lupus Erythematosus; im=intramuscular; iv=intravenous; JCA= Juvenile Idiopathic Arthritis; PU=Proctitis Ulcerosa; RA=Rheumatoid Arthritis; sc= subcutaneous; SLE=systemic lupus erythematosus; UC=Ulcerative colitis

Hydroxychloroquine and chloroquine

The use of hydroxychloroquine and chloroquine during pregnancy in small doses has shown to be safe. However, when larger doses are used for the treatment of acute malaria, oculotoxicity (eye) and cochlear (ear) toxicity have been reported.[7] Since 1990, several studies have investigated the safety of hydroxychloroquine and chloroquine during pregnancy (table 3), most describing its use in SLE. One study was performed in a randomized clinical setting[11], two studies describe a cohort comparing an exposed group to a non-exposed group[9;14]. The remaining studies[7,8,10,12,13] described a cohort exposed to hydroxychloroquine or chloroquine without a comparative group. None of the studies found an increased risk of congenital malformations. Most studies looked in detail for visual and hearing abnormalities, based on the suspicion of oculotoxicity and cochlear toxicity, but none of them found an increased association of these specific abnormalities with the use of hydroxychloroquine or chloroquine during pregnancy after a follow-up time varying from 9 months to 19 years. Five studies[9-11,13,14] concluded that hydroxychloroquine could be safely used during pregnancy in the treatment of SLE and advised the continuation of therapy during pregnancy rather than to discontinuation. However, it must be noted that there is no evidence to suggest any benefit from initiating hydroxychloroquine therapy during pregnancy.

Table 3. Disease Modifying Anti-Rheumatic Drugs and pregnancy: studies of hydroxychloroquine (HCQ) and chloroquine (CQ)

Author (country, year)	Study design	Pregnancy outcome	Comments
Levy, M. et al.[7] (Canada, 1991)	Exposed cohort to HCQ and CQ	27 pregnancies: 14 live births with no congenital abnormalities; 6 induced abortions; 4 spontaneous abortions; 3 stillbirths	Birth defects: all children are physically and developmentally normal with no clinical evidence of eye or hearing defects Indication: SLE (n=11), RA (n=3) or malaria prophylaxis (n=4) Follow-up: between 9mo and 19y (mean 5.3y) Co-medication: Prednisone, aspirom (acetylsalicyclic acid, ibuprofen, azathioprine, phenytoin, levothyroxine and penicillamine Exposure: only in first trimester Miscellaneous: more patients were on CQ (n=16) than on HCQ (n=8). For 18 women, representing 21 pregnancies, detailed information was reported, further information for the 6 women (6 pregnancies) with an induced abortion was not available
Buchanan, N. et al.[8] (UK, 1992)	Exposed cohort to HCQ (from larger cohort)	8 pregnancies: 5 live births with 2 live births with neonatal lupus; 1 fetal loss	Birth defects: none presented fetal malformations Indication: SLE (n=8), arthritis (n=7) Follow-up: a 4-year period for 76 patients, no detailed information on these 8 pregnancies Co-medication: azathioprine, prednisolone and aspirin Exposure: average: 20wk (range 1-39); 200 mg/day (n=6) or 400 mg/day (n=2) Miscellaneous: larger cohort included 100 consecutive pregnancies in 76 women, of which 8 received HCQ.
Parke, A. et al.[10] (USA, 1996)	Exposed cohort to HCQ	9 pregnancies: 9 live births	Birth defects: to date no visual or hearing abnormalities have been reported and development appears normal Indication: SLE Follow-up: mean 33mo; routine examinations have not been done in all children Co-medication: prednisone, subcutaneous heparin and asparin Exposure: throughout pregnancy; 200 mg/day or 200 mg every other day Miscellaneous: It is safer to continue HCQ rather than to discontinu because of pregn ancy

Author (country, year)	Study design	Pregnancy outcome		Comments
Buchanan, N. et al.[9] (UK, 1996)	Controlled cohort taking HCQ	Reference (53)	*Exposed (36)*	Birth defects: no evidence of visual disturbance was observed. Indication: cutaneous rash (n=33), arthritis (n=18) and serositis (n=1) in SLE (n=31) and DLE (n=2) patients Follow-up: no information Co-medication: azathioprine, prednisolone Exposure: mean 24.4mo (atenatal) and 28.4wk (pregnancy); 200 mg/day (n=22) or 400mg/day (n=14) at some point during gestation Miscellaneous: HCQ continuation is probably safe during pregnancy in patients with lupus, but there is no obvious advantage in commencing treatment.
		32 live births (1 twin), 1 Down's syndrome; 2 spontaneous abortions; 3 stillbirths	44 live births,1 with an extra finger; 4 spontaneous abortions; 5 stillbirths	
Klinger, G. et al.[12] (Canada, 2001)	Exposed cohort to HCQ (14) or CQ (7)	21 pregnancies, 21 live births (one twin), 1 with congenital birth defect, 1 spontaneous abortion		Birth defects: no visual or ophthalmological abnormalities in any of the exposed children. Indication: SLE or RA Follow-up: ophthalmological examination at mean 2.8 ± (SD) 2.9y Co-medication: no information Exposure: mean: 7.2 ± 2.9mo; 317 ± 109 mg/day (HCQ), 332 ± 116 mg/day (CQ) Miscellaneous: recruiting: through the Mother Risk Programme (Canada). Inclusion criteria: a minimum of 1 month's exposure to a daily dose of CQ or HCQ during pregnancy
Levy, R. et al.[11] (Brazil, 2001)	Randomized controlled study receiving HCQ or placebo	20 pregnancies Receiving HCQ: 10 live births, Receiving PL: 9 live births; 1 died after delivery at 25 weeks of gestation		Birth defects: clinical examination was normal and no auditory deficit occurred. Examination of both eyes was normal in all children. Indication: HCQ: (8 with SLE; 2 with DLE); placebo (9 with SLE; 1 with DLE) Follow-up: examination at age 1.5 – 3 years Co-medication: prednisone and aspirin Exposure: mean 11 wk (start) to 12 wk after delivery Miscellaneous: HCQ is safe in pregnancy with SLE. Final prednisone dosage was decreased in HCQ recipients and increased in placebo recipients

Author (country, year)	Study design	Pregnancy outcome		Comments
Motta, M. et al.[13] (Italy, 2002) Comment on Klinger et al.	Exposed cohort to HCQ	35 pregnancies: 35 live births, no congenital malformations		Birth defects: no baby had ocular symptoms or complications because of maternal treatment Indication: SLE (n=19), scleroderma (n=3), undifferentiated CTD (n=2), mixed CTD (n=4), dermatomyositis (n=1), primary antiphospholipid syndrome (n=4) and RA (n=1) Follow-up: an ophthalmological assessment was done at birth and again at 1y in 16 infants Co-medication: no information Exposure: 200 mg/day for ≥1 year before pregnancy and throughout gestation Miscellaneous: data seems to confirm safety of HCQ treatment
Costedoat-Chalmeau et al.[14] (France, 2003)	HCQ cohort	*Exposed (133)* 117 live births; 3 malformations; 15 spontaneous abortions; 1 fetal death; 0 induced abortions	*Reference (70)* 59 live births; 4 malformations; 7 spontaneous abortions; 2 fetal death; 2 induced abortions	Birth defects: no visual, hearing, growth, or developmental abnormalities were reported. Indication: SLE (69 exposed, 41 control), miscellaneous/unclassified CTD (n=13/4), primary Sjögren's syndrome (n=8/8) Follow-up: mean age 26mo (range 12-108mo) Co-medication: Prednisone (n=108/56), aspirin (n=112/54), low molecular weight heparin (n=35/13), azathioprine (n=2/2), intravenous immunoglobulin (n=2/0) Exposure: HCQ ≥6 month prior to pregnancy and continued throughout gestation; 200 mg twice daily (n=122), 200 mg/day (n=11) Miscellaneous: There findings support preliminary evidence for the safety of HCQ during treatment

HCQ= hydroxychloroquine; CQ=chloroquine; SLE=Systemic Lupus Erythematosus; DLE=Discoid Lupus Erythematosus; RA=Rheumatoid Arthritis; CTD=connective tissue disease; PL=placebo

Methotrexate

The use of methotrexate during pregnancy is described primarily in case reports, although a few studies described an exposed cohort. Kozlowski et al.[15] found no congenital anomalies among five live-born children in a cohort of ten pregnancies, but the rate of spontaneous abortions was rather high (three of ten pregnancies). Østensen et al.[22] reviewed four cases of methotrexate use during pregnancy. They found three live-born children without congenital malformations, and one woman had a miscarriage. Lewden et al.[27] described 28 pregnancies exposed to methotrexate and found 19 live births, of which one had minor neonatal anomalies, five were elective abortions and four were spontaneous abortions. Donnenfeld et al.[17] showed, in a series of case reports, ten healthy live-births and four first trimester spontaneous abortions (it was not reported if an autopsy was performed). The remaining case reports all reported fetuses with minor or major anomalies [18-21,23-26] (table 5) except for Feldkamp et al.[16] who described a healthy live birth. Feldkamp et al.[16] considered that a critical period of exposure to methotrexate (>10 mg weekly) exists at 6-8 weeks after conception. Regarding the high rate of spontaneous abortions seen in the studies mentioned previously, [15,17,22,27] it must be noted that methotrexate occasionally is used as an abortifacient in the management of an ectopic or unwanted pregnancy.[20]

Table 4. Disease Modifying Anti-Rheumatic Drugs and pregnancy: studies of methotrexate (MTX)

Author (country, year)	Study design	Pregnancy outcome	Comments
Kozlowski, R. et al.[15] (1990, USA)	Exposed cohort	10 pregnancies: 5 live-born infants; 3 spontaneous abortions; 2 elective abortions	Birth defects: none of the children exhibited congenital abnormalities. Indication: definite or classical adult RA (n=6); polyarticular juvenile RA (n=1); allergic angiitis (n=1) Follow-up: mean 11.5y (range 3.7 - 16.7y). Co-medication: aspirin, NSAIDs, HCQ, gold preparations, cytotoxics Exposure: 7.5 or 10 mg/wk orally. All patients stopped MTX within 1st trimester; one was exposed until 15th week of gestation. Miscellaneous: Data extracted from patients who unknowingly became pregnant; details gathered by telephone interview. Selection criteria: receiving MTX from January 1961 to July 1986.
Feldkamp, M. et al.[16] (1993, USA)	Case report	1 healthy live birth	Birth defects: a healthy full-term male infant was born Indication: RA Follow-up: examination at age 12wk Co-medication: ibuprofen, misoprostol, cimetadine or sucralfate (chronic), cefaclor, oxycodone, aspirin (short) Exposure: time from conception to discontinuation of MTX was minimal 3d to maximal 39d gestation; 7.5 mg/wk Miscellaneous: This case report was followed by a literature review
Donnenfeld, A. et al.[17] (1994, USA)	Case reports	14 pregnancies: 10 healthy live births; 1 with cavernous hemangioma; 4 first trimester spontaneous losses	Birth defects: one child with cavernous hemangioma Indication: RA (n=7), cancer (n=2), bacterial infection (n=1), psoriasis (n=1), unknown (n=3) Follow-up: no information Co-medication: aspirin, plaquenil, prednisone, dactinomycin, other chemotherapeutic agents Exposure: within 1y of conception or during pregnancy. Miscellaneous: the small number of patients in this sample precluded any conclusions regarding whether an association exists between preconceptional methotrexate exposure and spontaneous pregnancy loss. Data obtained through questionnaires using data from the teratogen information services (OTIS and ENTIS).

Author (country, year)	Study design	Pregnancy outcome	Comments
Buckley, L. et al. [18] (USA, 1997)	Case report	1 live birth infant with multiple congenital anomalies	Birth defects: the congenital abnormalities described are typical seen with exposure to an antifolate and include facial, skeletal, and cardiac abnormalities. Indication: polyarticular juvenile RA Follow-up: infant died at age 6mo Co-medication: folic acid, NSAIDs, gold Exposure: total dose of ~100 mg over a period of 8wk. Miscellaneous: an autopsy was not performed
Del Campo, M. et al. [19] (USA, 1997)	Case report	1 live birth infant with multiple congenital anomalies	Birth defects: fetal aminopterin/MTX syndrome and developmental dely Indication: chronic severe psoriasis Follow-up: 2y and 10mo Co-medication: none taken Exposure: 12.5 mg MTX 3 times weekly; throughout the first 8wk post-conception Miscellaneous: no information
Bawle, E. et al. [20] (USA, 1998)	Case reports	3 pregnancies: 3 live births, all with anomalies	Birth defects: fetal MTX syndrome (case 1); mild manifestation of fetal MTX syndrome (case 2 and 3) Indication: Termination of pregnancy (case 1 and 3); cancer (case 2) Follow-up: 26 y (case 1); 9y (case 2); 3.5y (case 3) Co-medication: 5-fluorouracil and radiation therapy (case 2) Exposure: 6 wk post-conception (case 1); 7.5wk till 28.5wk post-conception (case 2); 11-23wk post-conception (case 3) Miscellaneous: early psychomotor development was normal (case 1 and 3); ‘mentally deficient’ to low ‘borderline’ limits of intelligence compared with other students his age (case 2)

Author (country, year)	Study design	Pregnancy outcome	Comments
Østensen, M. et al. [22] (Norway, 2000)	Exposed cohort	4 pregnancies: 3 live births; no congenital malformations; 1 miscarriage	Birth defects: children have developed physically and mentally normal to their present age Indication: psoriatic arthritis; juvenile chronic arthritis; RA Follow-up: 1mo; 8mo; 5y Co-medication: naproxen, folate (at time of conception) Exposure: median 4y; between 5 mg and 15 mg weekly Miscellaneous: Miscarriage at wk 8, congenital malformations not investigated.
Krähenmann, F. et al. [23] (Switzerland, 2002)	Case report	1 terminated pregnancy: fetus with multiple malformations	Birth defects: fetus was diagnosed non-chromosomally caused AVSD and congenital diaphragmatic hernia Indication: RA Follow-up: pregnancy was terminated at 19wk Co-medication: folic acid (irregularly) Exposure: at wk 4+6d and wk 5+6d of gestation: 2x10 mg injections Miscellaneous: no information
Nguyen, C. et al. [24] (USA, 2002)	Case report	1 terminated pregnancy: fetus with multiple internal and external malformations	Birth defects: multiple internal and external malformations Indication: psoriasis Follow-up: elected termination at 20wk Co-medication: sertraline Exposure: 7.5 mg/day orally for 2d at 3.5wk post-conception Miscellaneous: fetopsy revealed craniofacial , axial skeletal, cardiopulmonary, and gastrointestinal abnormalities
Granzow, J. et al. [25] (USA, 2003)	Case report	1 live birth with an incomplete cleft palate and associated asymmetric deformities of the toes on both feet	Birth defects: incomplete cleft palate and associated asymmetric deformities of the toes on both feet Indication: management of a molar pregnancy Follow-up: at 38d Co-medication: no information Exposure: approximately the 8thwk of gestation Miscellaneous: no information

Author (country, year)	Study design	Pregnancy outcome	Comments
Giannakopou-lou, C. et al. [21] (Greece, 2000)	Case report	1 live birth with only minor malformation	Birth defects: an inguinal hernia was diagnosed Indication: cancer Follow-up: growth and development, up to the 22nd month, are normal Co-medication: cyclophosphamide and 6-fluorouracil Exposure: during 1st and 2nd trimester. Miscellaneous: no information
Chapa, J. et al. [26] (USA, 2003)	Case report (MTX)	1 terminated pregnancy: fetus with fetal anomalies	Birth defects: absent or markedly shortened long bones; abnormal positioning of the hands; micrognathia; echogenic bowel and two-vessel umbilical cord Indication: failed pregnancy termination Follow-up: pregnancy termination at 26wk Co-medication: misoprostol Exposure: at 6 wk; 75 mg intramuscular Miscellaneous: no information
Lewden, B. et al. [27] (France, 2004)	Exposed cohort to MTX	28 pregnancies: 19 live births; 1 minor neonatal anomalies; 5 elective abortions; 4 spontaneous abortions	Birth defects: one child with minor anomalies; metatarsus varus and eyelid angioma Indication: RA, Takayasu's arthritis, psoriatic arthritis and dermatomyositis or ankylosing spondylitis Follow-up: exposure between: 1993 and 2001 Co-medication: NSAIDs and corticosteroids Exposure: mean 10.5 mg/wk, discontinuation during first 4wk (n=16); still treated between 5 and 8wk (n=10); stopped after 8wk (n=1); from wk 6 to 11 (n=1) Miscellaneous: no strong teratogenic risk is associated with low dose MTX, provided that the drug is discontinued as early as possible in

MTX=methotrexate; AVSD= Atrioventricular Spetal Defect; RA=rheumatoid arthritis; NSAIDs=Non Steroidal Anti-Inflammatory Drugs; HCQ=hydroxychloroquine; OTIS=organization of Teratology Services; ENTIS=European Network of Teratology Information Services

The guidelines of the American College of Rheumatology advice a female patient, using methotrexate to wait at least one ovulatory cycle after discontinuation of methotrexate therapy before attempting to conceive because of its teratogenic potential.[1] The evidence regarding safety of methotrexate during pregnancy is conflicting, although a critical period and dose for exposure are proposed. The high rate of pregnancy losses indicates a risk to the fetus and, therefore, in each individual patient, consideration regarding the use of methotrexate before as well as during pregnancy has to be made. However, some situations, such as exposure after the first trimester in a severe case of RA, may lead to the conclusion that the benefits of using methotrexate to control disease activity may outweigh the potential risks. Although some healthy pregnancies have occurred after early methotrexate exposure, recommendations to stop methotrexate as soon as a pregnancy is discovered are in order. Clinical research is warranted to determine the delay between cessation of methotrexate and save conception.

Sulfasalazine

A population based case control study (based on 22,865 malformed offspring and 38,151 healthy controls) by Nørgård et al.[29] showed no increased prevalence of congenital malformations among children born to women treated with sulfasalazine during pregnancy. The reported use of sulfasalazine during pregnancy was low (0.07%). Källén et al.[30] studied children with orofacial clefting (n=1044) extracted from a large birth registry (n=576,873) and observed three cases of sulfasalazine use during pregnancy (risk ratio(RR)=3.0;95% CI: 0.62-8.77). Among the total population he found 515 users of sulfasalazine. In contrast, Koyama et al.[28] described a case of a neonate with holoprosencephaly, born to a woman with a continuous sulfasalazine treatment before and during pregnancy. It was the first case report of this type of malformation after sulfasalazine use. The above described sulfasalazine studies (summarized in table 6) are in accordance with its FDA pregnancy-risk category B; no major teratogenic effects of sulfasalazine were seen, although the risk of teratogenic events can not be excluded.

Azathioprine/6-Mercaptopurine

One case report by Oefferlbauer-Ernst et al.[36] showed one healthy child after exposure to azathioprine in utero. Francella et al.[35] studied 6-mercaptopurine, an active metabolite of azathioprine, and found no statistical differences for major malformations and some other outcomes. The authors concluded that before conception, at conception, or during pregnancy this drug appeared to be safe. Ramsey-Goldman et al.[32] reported on several immunosuppressive drugs being used before or during pregnancy; azathioprine was the only drug administered during pregnancy. Although they found the overall survival of women using immunosuppressive drugs prior to or during pregnancy encouraging, they questioned their safety and long term mutagenic effects. Heneghan et al.[33] and Alstead et al.[31] studied an exposed cohort, selected from a larger cohort, and concluded that the use of azathioprine during pregnancy appears to be generally safe. Nørgård et al.[34] reported the only study showing an increased risk of malformations although this could be confounded by disease activity. The above studies are summarized in table 6.

Table 5. Disease Modifying Anti-Rheumatic Drugs and pregnancy: studies of sulfasalazine (SSZ)

Author (country, year)	Study design	Pregnancy outcome	Comments
Koyama,N. et al.[28] (Japan, 1996)	Case report	1 neonate with holoprosencephaly	Birth defects: dysmorphic features: microcephaly; flat nosep; median clefts of lip and palate and hypotelorism. Indication: CD Follow-up: Child died at 6 mo Co-medication: ferostatin, kernac (plant), and protective drug for gastritis or gastric ulcer Exposure: before and during pregnancy; 3 g/day Miscellaneous: autopsy was not undertaken; Pregnancy occurred after treatment with human menopausal gonadotropin, chorionic gonadotropin and artificial insemination.
Nørgård,B. et al.[29] (Hungary, 2001)	Case control (population based)	22,865 malformed offsprings; 38,151 healthy controls. Exposed to SSZ: 17 cases; 26 controls	Birth defects: they found no significant increased prevalence of selected congenital abnormalities in the children of women treated with SSZ during pregnancy Indication: CD or CU (except one control) Follow-up: 1980-1996 Co-medication: concomitant drug use was not analyzed separately because of insufficient numbers of women without co-medication Exposure: 1st, 2nd and 3rd trimester; 4-8 g/day orally Miscellaneous: based on either self reported use or logbook information. Autopsy was obligatory for all death infants and was usual in still-born fetuses during the study period
Källén, B. [30] (Sweden, 2003)	Case control	Population: 576,873 (Medical Birth Registry) Identified orofacial cleft: 1044 SSZ exposure in population: 515 SSZ exposure among orofacial cleft: 3 (observed)	Birth defects: in Sweden maternal drug use is not a major contributor to orofacial clefts Indication: CU and CD (for three cases) Follow-up: July 1995 through December 2001 Co-medication: glucocorticoids and naproxen (for 1 of 3 cases) Exposure: first trimester Miscellaneous: risk ratio (observed/expected) 3.0 (95%CI: 0.62-8.77); orofacial cleft rate: 18.1 per 10,000 births (1044/ 576,873). Data were collected prospectively

CD=Crohn's Disease, CU=Colitis Ulcerosa

Table 6. Disease Modifying Anti-Rheumatic Drugs and pregnancy: studies of azathioprine/6-mercaptopurine (AZA/6-MP)

Author (country, year)	Study design	Pregnancy outcome	Comments
Alstead, E. et al.[31] (UK, 1990)	Exposed cohort	16 pregnancies: 15 live births (one twin); no congenital abnormalities; 2 terminated	Birth defects: all alive and well Indication: CD (n=14) or CU (n=2) Follow-up: 6mo to 16y Co-medication: prednisolone (n=12); sulfasalazine (n=6); mesalazine (n=1); codeine phosphate (n=1) Exposure: 7 women continued AZA throughout pregnancy; 5 stopped before 16 wk Miscellaneous: AZA appears not to be harmful to the fetus in early or late pregnancy in humans in doses used in IBD
Ramsey-Goldman, R. et al.[32] (USA, 1993)	Exposed cohort (from larger cohort)	9 pregnancies: 8 live births (one twin); no congenital malformations; 1 neonatal death; 1 miscarriage	Birth defects: no congenital malformations in infants exposed to AZA during pregnancy Indication: SLE Follow-up: mean 6.1y (range 1.5-13 y) Co-medication: no information Exposure: prior to pregnancy (n=5) and prior, as well as during, pregnancy (n=9) Miscellaneous: Final study group consists of 334 women. 14 patients (23 pregnancies) were exposed before or during pregnancy to AZA (n=9) or CsA (n=3) or MTX (n=1) or combined AZA and CsA (n=1). Only AZA was administered during pregnancy
Heneghan, M. et al.[33] (UK, 2001)	Exposed cohort to AZA, Pred and CsA (from larger cohort)	31 live births: 2 abnormalities; 1 fetal death (25 weeks); 1 fetal loss (20 weeks); 1 termination; 2 miscarriage	Birth defects: Perthes' disease, severe mental and physical handicap (neither mother received AZA) Indication: AIH Follow-up: median 10y (range 1.5-16y). Co-medication: prednisolone and cyclosporine Exposure: (conception) AZA 1 mg/kg/day (n=2) or 2 mg/kg/day (n=4); AZA 1 mg/kg/day (n=8) or 2 mg/kg/day (n=1) + prednisolone; prednisolone only (n=7), cyclosporine (n=1) Miscellaneous: AZA appears to be generally safe and without adverse outcomes

Author (country, year)	Study design	Pregnancy outcome		Comments
Nørgård, B. et al. [34] (Denmark, 2003)	Cohort AZA (or 6-MP)	*Exposed* 11 live births: 2 malformations (1 died)	*Reference* 19.418 live births: 711 malfor-mations	Birth defects: aphakia and multiple malformations Indication: CU; CD; myasthenia; vasculitis; IgA nephritis; AIH; glomerulonephrtitis and renal transplant Follow-up: no information Co-medication: prednisolone, cyclosporine, ursodeoxycholic acid, antihypertensive drugs Exposure: (variable) 30d before conception to third trimester Miscellaneous: odds ratio for malformation = 6.7 (95%CI:1.4-32.4). The data indicate a increased risk of malformations, associations could be confounded by disease activity. Study period: 1 January 1991 to 31 December 2000.
Francella, A. et al. [35] (USA, 2003)	Exposed cohort to 6-MP (from larger cohort)	39 pregnancies: 32 live births; 1 major birth defect; 3 minor birth defects; 5 spontaneous abortions; 1 elective abortion; 1 miscarriage		Birth defects: there was no statistical difference in major congenital malformations among male or female patients taking 6-MP compared with controls Indication: IBD Follow-up: minimum 18mo from birth. Co-medication: antibiotics, sulfasalazine, mesalamine, systemic and local corticosteroids, antidiarrheals, and antispoasmodcs. Exposure: cohort exists of females (f) and males (m), divided into 4 groups: A: 6-MP before conception (f/m), B1: 6-MP at time of conception (f/m), B2: During entire pregnancy (f), C: pregnancies before 6-MP treatment (f/m). Miscellaneous: 6-MP use before or at conception or during pregnancy appears to be safe
Oefferlbauer-Ernst, A. et al. [36] (Austria, 2004)	Case repor	1 healthy baby		Birth defects: healthy baby Indication: CD Follow-up: no information Co-medication: no information Exposure: therapy at conception and throughout pregnancy Miscellaneous: discontinuation of AZA and 6-MP treatment seems to be not longer indicated if planning a pregnancy

CD=Crohn's Disease; CU=Colitis Ulcerosa; AIH=Autoimmune Hepatitis; IBD=Inflammatory Bowel Disease; SLE= Systemic Lupus Erythematosus

Miscellaneous Disease Modifying Anti-rheumatic Drugs

Biologicals

Adalimunab

Information on the effects of adalimumab (approved by the FDA in 2003) in human pregnancy were not found during the search. The product leaflet declared that there was no indication from an animal study for maternal toxicity, embryo toxicity or teratogenicity.[37]

Infliximab

Information from a database maintained by the manufacturer showed 131 women exposed to infliximab during pregnancy[38], and outcome data were available for 96 women. Sixty-four pregnancies delivered a live-born child, miscarriage occurred in 14 pregnancies and 18 pregnancies underwent elective abortion. Srinivasan et al.[39] reported an exposed cohort of 27 women exposed to infliximab immediately prior to or during the first trimester of pregnancy. Data was available for ten women; six women had live-born children, of whom one died a few days after birth, three reported a miscarriage, and one underwent an elective abortion.Burt et al.[40] reported one case of a woman receiving infliximab shortly after becoming pregnant; a healthy child was born and no neonatal abnormality were noted.Chakravarty et al.[41] reported two pregnancies exposed to infliximab; one healthy baby was born and one outcome was not stated.

Etanercept

Exposure to etanercept occurred in 15 pregnancies reported by Chakravarty et al.[41]. Six healthy children were born, four were still pregnant at time of the report, one had an elective abortion and one had a spontaneous abortion.

Anakinra

No information about the use of anakinra in pregnancy was found in literature. The prescribing information declared that no effect on early development, embryo-fetal development, or peri-and postnatal development was observed.[42]

Leflunomide

The active metabolite of leflunomide is teratogenic in rats and rabbits and may cause fetal harm in humans.[43] Therefore, leflunomide must not be given in

pregnant women or women who wish to become pregnant. A safety update of the manufacturer of leflunomide[44] involving 310 exposures during pregnancy reported 164 exposed pregnancies of which the outcome was known. Forty-three pregnancies were terminated, 36 women had a miscarriage and 85 ended in a life birth (seven of whom were born with congenital malformations).

Cyclosporine

Although cyclosporine is a pregnancy-risk category C drug (meaning that animal studies either showed an adverse effect or not have been conducted and that there are no adequate and well controlled studies in pregnant women), a meta-analysis has been conducted by Bar Oz et al.[45] The authors concluded that the use of cyclosporine did not appear to be a major human teratogen. They found a non-significant odds ratio for malformations of 3.83 (95% CI, 0.75-19.6).

Cyclophosphamide

Since 1990, only a few cases have been reported the use of cyclophosphamide during pregnancy.[46-48] Cyclophosphamide is considered to be teratogenic and is classified as D in the pregnancy-risk category. Two cases reported a live-born child46,48, one case reported a child who died 12 days after birth and was diagnosed with a pattern of malformations referred to as cyclophosphamide embryopathy47 and one case reported an unknown outcome. In addition to their own case report, Vaux et al.[47] give an overview of all cases reported in literature between 1964 and 2003. In particular, they described craniofacial and limb defects and showed that all reported cases had similar patterns of malformations.

Gold preparations

No reports about the use of gold-preparations in pregnancy could be found after 1990. According to the product leaflets of aurothioglucose[49], auranofin[50], and gold sodium thiomalate[51], all showed teratogenic effects in animal studies. In the product leaflet of aurothioglucose, it was thought to be teratogenic in early human studies but later studies indicate that it might not be harmful. (this information could

not be confirmed by this literature search) Despite this, gold preparations are not recommended for use in pregnancy.[49]

Penicillamine

Since 1990, several case reports have been published on the use of penicillamine in human pregnancy.[52-61] Penicillamine is in the D in the pregnancy-risk category. All reported cases described the use of penicillamine in Wilson's disease, an inheritable autosomal recessive disorder of copper accumulation.[56] The results of the case reports are ambiguous, both healthy children and children with anomalies were born.

Discussion

This review underscores the gross absence of data on safety and risks of DMARD use during conception and pregnancy. Regulatory authorities, scientific society and rheumatologists and other specialists are obliged to dissuade the continuation of most DMARD if pregnancy is desired. Nevertheless, RA patients do become pregnant and sometimes continue drug use of DMARDs.

Since 1990, a limited number of studies on DMARD use during pregnancy were found. Apart from two large case-control studies (22,865 cases vs. 38,151 controls[29] and 1044 cases vs. 576,873 controls[30]) and one large cohort (19,430 women[34]), most studies are either small cohorts (ranging between 4 and 515 exposed women) or case-reports (ranging between 1 and 14 cases).

According to Mitchell[3], two main study approaches have been developed, with the purpose of identifying teratogens after marketing approval of a drug, i.e. follow-up studies and case-control surveillances. In follow-up studies, small numbers are sufficient to identify high-risk teratogens. But for drugs which have a moderate or low teratogenic potential, large numbers of exposed persons are needed, especially when the outcome is rare. Case-control studies have more substantial statistical power and are therefore more appropriate to identify moderate-teratogen drugs. Case-control studies can provide safety and risk estimates that become more precise as data accumulate.

The results for the use of methotrexate in pregnancy reconfirm the category X of the FDA categorization, stating that the possible risk clearly outweighs any positive benefit. The advice to wait at least one ovulatory circle after discontinuation of methotrexate before attempting to conceive remains valid. In contrast to the FDA categorization, this review suggests that hydroxychloroquine in moderate dosages can be safely used during pregnancy in the treatment of SLE or RA. However, these conclusions are based on small exposed cohorts. Azathioprine is categorized as a drug that, despite indications of fetal risks, can be considered during pregnancy if the benefits of therapy outweigh the potential risks. The results of this review are in line with this advice and conclude that azathioprine seems to be generally safe in pregnancy. Only one large cohort was conducted, which found an increased risk for malformations, which could be confounded by disease activity.[34] It must be realized that for some drugs (e.g. sulfasalazine and azathioprine), information is limited to their use in rheumatic diseases; studies describing the use of these drugs for other indications may broaden the discussion but are not likely to change the conclusions found in this review.

Meijer et al.[62] and Hernandez-Diaz et al.[63] described the use of folic acid antagonists, but neither of them reported a protective effect of folic acid when methotrexate or sulfasalazine is used. Hernandez-Diaz et al.[63] showed a reduction of the OR of having an infant with a neural tube defect when carbamazepine or trimethoprim, both folic acid antagonist, were administered in combination with folic acid compared with women who received the drugs without folic acid.

Information about other DMARD is even more limited; studies are mostly based on case reports or small exposed cohorts. A recent study with respect to cyclophosphamide by Clowse et al.[64] showed that all four pregnancies exposed to cyclophosphamide resulted in first trimester miscarriage and thus confirming its category D pregnancy-risk status.

It must be noted that small studies are not powered to detect any moderate or low risk for birth defects. If, for example, a certain birth defect occurred in 1 of 1000 births, a sample size of approximately 600 can detect approximately a 20-fold or higher increase of that birth defect. However, none of the cohorts found in this

review had sample sizes >600 and are by definition to small to detect a small or moderate increase in the prevalence of specific birth defects.

Albrecht et al.[65] conducted a study evaluating the impact of case-series and case-reports describing innovative treatment published. They concluded that case-series and reports can be well received and have significant influence on subsequent literature and possibly on clinical practice. They reported that the case-reports and case-series they found in the Lancet were followed by a clinical trail in 17% and 33% of cases, respectively. Because pregnant women are usually excluded from clinical trials, case-reports and case-series are the first signals in clinical practice of an adverse effect or outcome after exposure to a drug. Ideally, these should be followed by a case-control surveillance or follow-up study. This review of the literature showed that although many case-reports, case-series, and small exposed cohorts did function as a signal for a possible adverse outcome, they were almost never followed by a case control surveillance or follow-up study. Perhaps more time is needed to collect enough data to conduct proper case-control surveillances or large cohort studies.

This review focused on recent literature, assuming that older information is taken into account by the construction of the pregnancy-risk categorization. Recent information on the influence of DMARD on pregnancy and pregnancy outcome is limited. This might be explained by the focus on the use of DMARD in rheumatic disease and the use of the drugs as monotherapy. Another reason might be the timing of the approval for a particular drug on the market. Drugs recently approved, such as etanercept and infliximab, are used for a selected group to whom existing therapy is not effective anymore. Clinical trials exclude pregnant women; therefore, it is to be expected that the information on these drugs is limited.

None of the studies reported on the relationship between exposure to the drug, genetic variability, and the effects of these genetic factors. This might not have been an issue when these studies were conducted; however, this will be an important factor in the future and therefore has to be considered.

Despite limited information on the influence of DMARD in pregnant women with a rheumatic disease, these drugs are used in practice and despite the advice to avoid pregnancy patients become pregnant while receiving DMARDs. Therefore,

we suggest that a good monitoring system for DMARD use during pregnancy, which reports all pregnancies irrespective of pregnancy outcome, could be of great help to contribute to the research of possible teratogenity of DMARDs In addition, it could help to provide more solid information to patients and health care professionals in RA treatment.

Conclusion

In conclusion, this review underscores the gross absence of data on safety and risks of DMARD use during conception and pregnancy. Clinicians working with young patients using DMARDs are obliged to dissuade the continuation of most DMARDs in case pregnancy is desired. Nevertheless, this review shows that RA patients become pregnant and sometimes continue drug use and therefore, further research on the safety and risks of these drugs during pregnancy is necessary.

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Chapter 2

Prescribing of NSAIDs and ASA during pregnancy; do we need to be more careful?

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Summary

Aim

This study examines the extent of NSAID and/or ASA prescribing around and during pregnancy.

Methods:

Mothers extracted from iadb.nl (population-based prescription database, 1995-2004), of whom we had drug information three months before conception till three months after delivery, were identified.

Results:

In 3.9% of the pregnancies (N=557) a NSAID (ATC-code: M01A) and/or ASA (ATC-code: N02BA) were prescribed during pregnancy, 2.9% (N=421) received a prescription during first trimester.

Conclusion:

NSAIDs and ASA are prescribed during the first trimester of pregnancy. Future studies are needed to see the effects of the recent warning of the EMEA on prescribing of NSAIDs or ASA.

Introduction

Use of drugs during pregnancy is and always will be a delicate issue for clinicians and mothers-to-be. With respect to non-steroidal anti-inflammatory drugs (NSAIDs) and Acetylsalicylic acid (ASA), it is recommended not to use both drugs during the third trimester of pregnancy. These recommendations were formulated based on effects such as increased risk of premature closure of the ductus arteriosus[1-2]. In 2005 European registration authorities (EMEA=European Medicines Agency) warned about use of NSAIDs and ASA during first trimesters of pregnancy; NSAIDs and ASA should not be used during first trimesters of pregnancy except when this is strictly indicated[3]. This warning was based on recent studies describing associations between NSAIDS and/or ASA use and congenital heart defects[4-7], gastroschisis[8-11], neural tube defects[10] and orofacial clefts[5;10]. Although the studies were not conclusive for most congenital malformations, with respect to gastroschisis most studies found an increased risk[8-11].

Little is known about prescribing of NSAIDs and ASA in daily practice, therefore this study will described to which extend NSAIDs and ASA are prescribed during pregnancy.

Method

Setting

This study was performed using pharmacy dispensing data from IADB.nl (population-based database) in Northern and Eastern Netherlands[12]. In 2003, IADB.nl contained prescriptions from an estimated population of 500.000 individuals. Each prescription record contains among others name of the drug, date of dispensing, amount dispensed, dose regimen and all drugs are coded according to the Anatomical Therapeutic Chemical (ATC)-classification[13]. Date of birth and gender of each patient are available and all patients have an unique anonymous identifier. Due to high patient-pharmacy commitment in the Netherlands and sophisticated pharmacy software, medication records for each patient are virtually complete[12]. This database comprises all prescription drugs, excluding drugs dispensed during hospitalizations and OTC drugs.

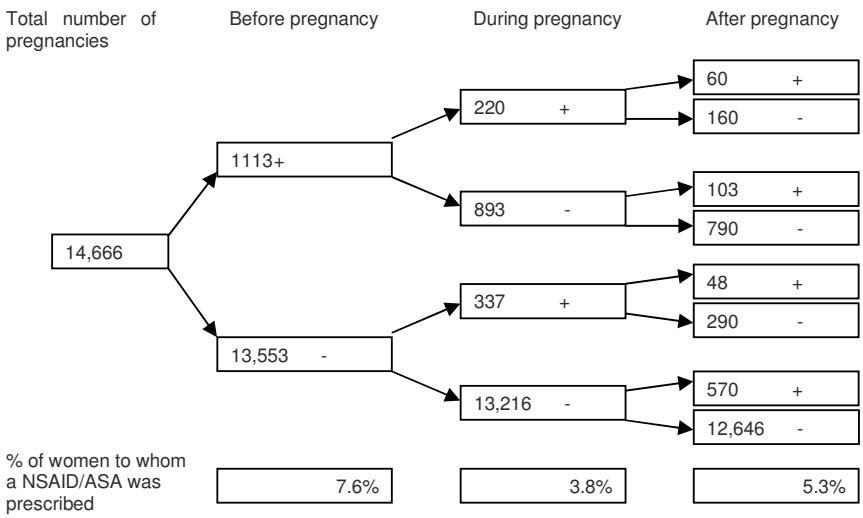
Study population and design

The pregnancy-IADB.nl (1995-2004) was extracted from the main IADB.nl database. Children were selected by date of birth and by using an address-code the mother of this child was identified. This method is validated and described by Schirm et al.[14]. The gestational age is calculated for every mother by subtracting 273 days (3 trimesters of 91 days, approx. 9 months) from birth date of the child; this date will be referred to as conception. The period between conception and birth date of the child will be considered as gestation and is per definition 273 days. We included all mothers of whom we had drug information about the defined time-window of three months before conception till three months after delivery. All women to whom NSAIDs (ATC-code: M01A) and/or ASA (ATC-code: N02BA) were prescribed at some point during this time-window were selected (N=2020), small dose ASA-preparations (ATC: B01AC06/08) were excluded. We calculated prevalence before, during and after pregnancy based on exposure rate. Exposure rate is defined as the number of pregnancies in which in theory a women has availability to a drug or class of drugs, i.e. those who received a prescription in one trimester which was extended into the next trimester, are counted for both trimesters in which they had access to the drug[15].

Results

From the IADB.nl (1995-2004), 14,666 pregnancies were identified, in 13.8% (N=2020) NSAIDs or ASA were prescribed in the time-window three months before pregnancy till three months after delivery. Among those users 96% received a NSAID and less than 5.5 % were prescribed ASA, approximately 1.5% received both drugs. Diclofenac, Ibuprofen and Naproxen are the most prescribed NSAIDs. Average age at time of delivery of women to whom a NSAID or ASA was prescribed (29.74 years, range 16-49) did not differ of those without having prescribed these drugs (29.91 years, p=0.077).

Figure 1 shows the number of pregnancies in which NSAIDs and/or ASA were prescribed in the investigated time-window. In 7.6% (1113/14,666) of the pregnancies these drugs were prescribed before conception, in 3.8% (557/14,666) during gestation and in 5.3% (781/14,666) after pregnancy.



+ Women to whom a NSAID and or ASA was prescribed during that period,
- Women who did not receive a NSAID and/or ASA during that period

Figure 1. Number of pregnancies in which a NSAID and/or ASA was prescribed before, during and after pregnancy.

Women to whom NSAIDs and/or ASA were prescribed during gestation, 61% (337/557) started these drugs for the first time during gestation (in the investigated time-window). The drugs were restarted by 13% (103/781) after discontinuation during pregnancy and 73% (570/781) started it for the first time after delivery during the investigated time window.
In 557 pregnancies NSAIDs and/or ASA were prescribed during gestation, 2.9% (421/14,666) received it during first trimester, in the second and third trimester this was 0.74% (N=108) and 0.64% (N=94) respectively.

Discussion

This study reports on NSAID and ASA prescribing before, during and after pregnancy in a population-based database. In 3.9% of the pregnancies NSAIDs and/or ASA are prescribed during pregnancy, in 2.9% NSAIDs and/or ASA are

being prescribed during first trimester. Our data does not contain information about OTC-use or sales and therefore the results found in this study underestimate actual use. Unpublished data of the EUROCAT-registration Northern-Netherlands showed that 60% received a prescription for NSAIDs approx. 35% retrieved their NSAID OTC.

Prescribing of NSAIDs and/or ASA during third trimester is low (0.6%) which was to be expected due to existing guidelines not to prescribe these drugs during the third trimester. In 2005 a warning from the EMEA stated that NSAIDs and/or ASA should not be used during the first trimesters of pregnancy unless this was strictly indicated. This warning was based on studies showing increased associations with among others gastroschisis[8-11]. Our data showed low prescribing of NSAIDs during the second and third trimester being 0.7 and 0.6% respectively, but prescribing during the first trimester was much higher (2.9%).

In the Netherlands approx. 200.000 children per year are born [16], approx. 1 per 5000 children[17] is born with gastroschisis. If 3% of the pregnant women are prescribed NSAIDs (or ASA) during first trimester, approx. 6000 pregnant women are eligible for exposure to these drugs in that period. If we assume an OR of 4.0 on the risk of gastroschisis, found by Torfs et al.[11] to be true, 4.8 children (6000*4/5000) with gastroschisis will be born among the women using NSAIDs and/or ASA. Based on the data from EUROCAT we can assume that the 3% found in the IADB.nl will be an underestimation of actual use.

We do realize this data represent prescribing of NSAIDs and/or ASA before the warning from the EMEA. However, we strongly recommend that prescribing physicians have to be careful in prescribing these drugs to women in the fertile age, especially when use of these drugs during pregnancy increases the risk of certain birth defects such as gastroschisis. If the warning of the EMEA will result in less prescribing of NSAIDs and/or ASA, especially during first trimester of pregnancy, has to be examined in future research.

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Chapter 3

Prescribing of sulfasalazine, azathioprine and methotrexate round pregnancy – a descriptive study.

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Abstract

Purpose: Continuation or discontinuation of drugs during pregnancy in chronic diseases is an issue of concern. Information on prescribing of Disease Modifying Anti-Rheumatic Drugs (DMARDs) during pregnancy is scarce. In this study we report prescribing patterns round pregnancy of sulfasalazine (SSZ), azathioprine (AZA), methotrexate (MTX) and co-medications among women to whom one of these DMARDs were prescribed before pregnancy.

Methods: The pregnancy-Interaction Database (IADB.nl, 1994-2004), containing pharmacy dispensing data from northern-Netherlands, was used. Women to whom SSZ (N=13), AZA (N=10) or MTX (N=6) was prescribed before their first pregnancy were identified and described in detail.

Results: AZA and SSZ are continued during pregnancy by 60% and 38% of the women respectively, MTX was stopped before pregnancy. Among women receiving SSZ (N=13) as their initial DMARD, anti-inflammatory and anti-rheumatic drugs (69%) and analgesics (45%) were the most commonly prescribed co-medications. Among women receiving AZA (N=8) as their initial DMARD, corticosteroids for systemic use (100%) and intestinal anti-inflammatory agents (88%) were the most commonly prescribed co-medications. All women receiving intestinal anti-inflammatory drugs before pregnancy continued this during pregnancy, in contrast to other co-medications which were mainly discontinued.

Conclusions: Our study showed that DMARDs and co-medication are received before, during and after pregnancy, although no specific prescription patterns were found. Administrative database, such as the pregnancy-IADB.nl, are useful in describing drug prescribing patterns for better understanding of drug prescribing around pregnancy in daily practice. Based on this data we conclude that prescribing of DMARDs and related co-medication is based on the individual patient.

Introduction

In chronic inflammatory diseases such as rheumatoid arthritis (RA) and inflammatory bowel disease (IBD) drugs as sulfasalazine, azathioprine and methotrexate are commonly used to control the disease. Continuation or discontinuation of these drugs during pregnancy is balancing between relapse of the (chronic) disorder and the potential harm of the drug to the mother or foetus. Since young age and child wish often coincide, the use of drugs during pregnancy is an ever returning issue of concern for physician as well as for the mother to be. IBD typically presents itself at young age[1] and pharmacotherapy may be required to control the disease activity not only before but also during and after pregnancy. It is believed that disease activity of IBD plays a more important role in determining foetal outcome than drug therapy[2].

In the treatment of rheumatic diseases new therapeutic strategies have become available in the last decade. The application of Non-Steroidal Anti-Inflammatory Drugs (NSAID) for symptom control changed to the application of Disease Modifying Anti-Rheumatic Drugs (DMARDs) for disease control. These new understandings on DMARDs use have led to a change of treatment guidelines[3;4]. Especially in young people, diagnosed with a rheumatic disorder, prevention of joint damage will be a key issue of the treatment and currently a DMARD will be initialized early after diagnosis to prevent irreversible damage to the joints. While women with Systemic Lupus Erythematosus (SLE) frequently have symptoms of their disease during pregnancy, approximately 75% of the Rheumatoid Arthritis (RA) patients will experience improvement of their symptoms during pregnancy[5]. Therefore continuation or discontinuation of DMARDs during pregnancy has to be discussed by the physician and patient.

Several studies[6-11] have described the use of drugs in pregnancy in general. Prescription databases as well as studies using interviews as their main data source were used to describe drug use before, during or after pregnancy. Drug use during pregnancy (including or excluding vitamins or minerals) varied from 44% till 99%[11] between the different studies. Scarcely studies describe the use of a specific group of drugs during pregnancy such as corticosteroids[12], leflunomide[13], cyclophosphamide[14] or NSAIDs[15]. All these latter studies related the use of the

drugs to the outcome of the pregnancy. Most studies emphasize on the relation between drug use and pregnancy outcome. This study will emphasize on the pattern of drug prescribing among pregnant women who were dispensed sulfasalazine (SSZ), azathioprine (AZA), or methotrexate (MTX) at some point before their first pregnancy. If possible this drug prescribing pattern will be compared with available guidelines.

Method

Setting

This study was performed using pharmacy dispensing data from IADB.nl (a general prescription drugs database) in the Northern and Eastern parts of the Netherlands[16]. In 2003, the IADB contained prescriptions from an estimated population of 500.000 individuals. Each prescription record contains information about the drug, date of dispensing, amount dispensed, dose regimen and the prescribing physician and all drugs are coded according to the Anatomical Therapeutic Chemical (ATC)-classification[17]. Date of birth and gender of each patient are available and all patients have a unique anonymous identifier. In the Netherlands patients usually visit the same pharmacy. Due to this high patient-pharmacy commitment in the Netherlands and sophisticated pharmacy software, the medication records for each patient are virtually complete[16]. This database comprises all prescription drugs, excluding drugs dispensed during hospitalizations and OTC drugs.

For this particular study we used the pregnancy IADB (1994-2004), which contains data extracted from the main IADB database. Children were selected by date of birth and by using an address-code, the mother of this child was identified. This method is validated and described elsewhere by Schirm et al.[18]. The gestational age is calculated for every mother as a theoretical conception date by subtracting 273 days (3 trimesters of 91 days, approximately 9 months) from the birth date of the child; this date will be referred to as conception.

The period between conception and birth date of the child will be considered as the gestation and is per definition 273 days.

Study population and design

In 2004 the pregnancy IADB contains 12,177 women. To exclude effects of another pregnancy on drug prescribing and possible use, we choose to use only the first database-registered pregnancy of these 12,177 women.

Among the women to whom a DMARD (N=163) was prescribed at any time, we excluded those women who received only one prescription of hydroxychloroquine (HCQ) or chloroquine (CQ) and no prescriptions for another DMARD (N=57) because they were more likely to receive HCQ or CQ as a malaria prophylaxis than for control of an inflammatory disease. Women to whom a DMARD was prescribed only after pregnancy (N=71) were excluded as well.

Thirty-five women received a prescription for a DMARD before their first pregnancy (table 1), of these women we had information for at least one year before conception, the whole pregnancy and at least one year after pregnancy available. Women to whom one or more prescriptions for MTX, SSZ or AZA were dispensed will be described in this study.

The full medication histories of the women using MTX, SSZ and AZA have been selected, including name of the drugs, date of dispensing, ATC code, number of DDD (defined daily dose) [17] and the number of days it was prescribed for. The Prescribed Daily Dose (PDD), used to evaluate changes in dose, was calculated by dividing the number of DDD by the number of days it was prescribed for.

Table 1. Number of women receiving a DMARD before and during pregnancy

Drug	Before pregnancy	In pregnancy
Sulfasalazine (SSZ)	13 (37%)	5
Azathioprine (AZA)	10 (29%)	6
Methotrexate (MTX)	6 (17%)	0
Hydroxychloroquine (HCQ)	5 (14%)	0
Chloroquine (CQ)	4 (11%)	1
Cyclosporine (CSP)	1 (3%)	1#
Total	35 (111%)*	13

Woman used SSZ before pregnancy and started CSP in pregnancy

* Some women received more than 1 DMARD, one woman received SSZ and AZA, one woman received SSZ and MTX and one woman received SSZ, AZA and MTX before pregnancy

Because indications for the drugs are unknown in this prescription database we asked two clinical pharmacists to assign an indication to a woman, based on DMARD prescriptions in combination with co-medication. A possible indication was assigned only if both pharmacists agreed about the indication. Drugs are defined as co-medication if the drug can be prescribed for the same indication either a rheumatic disease or inflammatory bowel disease. Table 2 shows drugs (by partial ATC-code and group name) considered to be co-medication. Reporting of related co-medication (prescribed for more then 7 days) will start after the dispensing date of the first available DMARD prescription. Data on drugs dispensed as a primary product, used to prepare for example capsules or enama by hand, will not be reported. The drug prescribing found in the database will be compared with available guidelines.

Table 2. The ATC code and group name of drugs which are considered to be co-medication

ATC-code	Group name
A03A	Drugs for functional bowel disorders
A06	Laxatives
A07	Anti-diarrheals, intestinal anti-inflammatory/anti-infective agents
H02	Corticosteroids for systemic use
L04	Immunosuppressive agents
M01	Anti-inflammatory and antirheumatic products
N02A	Opioids
N02B	Analgesics and antipyretics

Results

In the pregnancy-IADB, almost three per 1000 pregnant women were prescribed a DMARD before pregnancy. The average age at birth of their first child is 30.7 years and all mothers delivered singletons. The average follow-up of these women was 103 months. Ten women were dispensed HCQ, CQ or Cyclosporin (CSP) before their first pregnancy, 25 women were given SSZ, AZA or MTX and are therefore eligible for analysis (table 1). Six women were dispensed MTX, thirteen women were given SSZ and ten women were dispensed AZA. Eight women were thought to have a rheumatic disease, twelve were thought to have IBD and for five women an indication could not be determined.

Sulfasalazine (n=10)

Table 3 shows that ten women were dispensed SSZ before conception as a single DMARD. Five women (50%) continued SSZ during pregnancy, one woman switch to cyclosporine. All women received co-medication before conception; most of them were dispensed an anti-inflammatory and anti-rheumatic drug (70%, N=7) or analgesic (50%,N=5).

Table 3. Dispensed DMARD and co-medications before, during and after pregnancy for women receiving a Sulfasalazine prescription as their initial DMARD before pregnancy.

nr	Possible Indication	Last pres-cription DMARD	Before conception			Pregnancy						One year after pregnancy	
						Trimester 1		Trimester 2		Trimester 3			
			Drugs prescribed[1]	PDD	Days (N)	PDD	Days (N)	PDD	Days (N)	PDD	Days (N)	PDD	Days (N)-
1	Rheu-matic disease	-	SSZ	0.50	1.25	1.00	50	-	-	-	-	0.50	10
			Paracetamol/ codeine	0.50	20	-	-	-	-	-	-	1.00	30
			Diclofenac			-	-	-	-	-	-	1.00	360
2	?	-	SSZ	1.00	90	1.00	90	-	-	1.00	90	0.60	20
			Loperamide	-	-	-	-	-	-	-	-	-	-
3	Rheu-matic disease	-	SSZ	1.20	50	1.50	20	-	-	-	-	-	-
			Meloxicam	1.00	120	1.00	30	-	-	-	-	-	-
			Indometacin	1.50	15	1.50	30	-	-	-	-	0.60	25
			Paracetamol	1.00	30	-	-	-	-	0.50	10	-	-
			Paracetamol/ codeine	1.00	10	-	-	-	-	-	-	-	-

Nr	Possible indication	Last prescrip-tion DMARD	Before concetption			Pregnancy						One year after pregnancy	
						Trimester 1		Trimester 2		Trimester 3			
			Drugs prescribed	PDD	Days (N)	PDD	Days (N)	PDD	Days (N)	PDD	Days (N)	PDD	Days (N)
4	Rheu-matic disease	-	SSZ	0.67	1133	1.50	60	0.99	68	1.50	90	1.00	360
			Prednisolone	-	-	-	-	0.50	60	0.50	120	1.00	360
			Piroxicam	1.14	210	-	-	-	-	-	-	1.43	63
			Paracetamol	0.58	49	-	-	-	-	-	-	-	-
5	Rheu-matic disease	-	SSZ	0.70*	698	1.00	50	1.00	15	-	-	1.00	30
			Naproxen	3.00	90	-	-	-	-	-	-	3.00	90
6	Rheu-matic disease	-	SSZ	1.00	300	-	-	-	-	-	-	-	-
			CSP	-	-	0.90	105	0.80	90	0.80	45	0.80	315
			MTX	-	-	-	-	-	-	-	-	0.21	420
			Indometacin	1.5	135	-	-	-	-	-	-	-	-
			Ibuprofen	1.25	64	1.25	56	1.33	98	-	-	-	-
			Diclofenac	0.75	90	-	-	-	-	-	-	2.00	320.
			Paracetamol	0.50	60	-	-	-	--	--	-	0.98	320

Nr	Possible indication	Last prescrip-tion DMARD	Before conception			Pregnancy						One year after pregnancy	
						Trimester 1		Trimester 2		Trimester 3			
			Drugs prescri-bed	PDD	Days (N)	PDD	Days (N)	PDD	Days (N)	PDD	Days (N)	PDD	Days (N)
7	Inflam-matory bowel disease	36 months	SSZ	2.08	24	-		-	-	-	-	-	-
			Budesonide	0.95	269	0.67	30	-	-	-	-	-	-
			Carbasalate caldium	0.50	5	-	-	-	-	-	-	0.66-	5
			Isphagula	0.56	150	-	-	-	-	-	-	-	-
			Ibuprofen	1.00	10	-	-	-	-	-	-	-	-
			Paracetamol	0.63	8	-	-	-	-	-	-	-	-
			Mesalsine	-	-	2.00	15	-	-	-	-	-	-
8	Inflam-matory bowel disease	9 months	SSZ	1.50	10	-	-	-	-	-	-	1.50	45
			Mesalazine O[2]	1.73	227	1.33	90	2.66	60	2.66	60	2.66	328
			Mesalazione R	-	-	-	-	158.4	93	158.4	56	158.4	63
			Prednisolone	-	-	-	-	-	-	1.77	65	0.50	40

Nr	Possible indication	Last prescrip-tion DMARD	Before concetption			Pregnancy						One year after pregnancy	
						Trimester 1		Trimester 2		Trimester 3			
			Drugs prescribed	PDD	Days (N)	PDD	Days (N)	PDD	Days (N)	PDD	Days (N)	PDD	Days (N)
9	Rheu-matic disease	7 months	SSZ	1.16	18.	-	-	-	-	-	-	-	-
			MTX	-	-	-	-	-	-	-	-	0.90	-93
			Rofecoxib	1.00	90	-	-	-	-	-	-	1.00	60
			Meloxicam	0.84	160	-	-	-	-	-	-	-	-
10	?	26 months	SSZ	0.50	41	-	-	-	-	-	-	-	-
			Diclofenac	1.50	10	-	-	-	-	-	-	-	-
Patients receivind SSZ in combination with other DMARD													
11	Rheu-matic	3 months	SSZ	1.10	600	-	-	-	-	-	-	1.00	180
			MTX	1.15	61	-	-	-	-	-	-	-	-
			Ibuprofen	1.00	60	1.00	30	0.33	30	-	-	0.33	140
			Indometacin	1.50	950	-	-	-	-	-	-	1.50	300
			Dextroprop oxy phene	0.75	210	-	-	-	-	-	-	0.75	60

Nr	Possible indication	Last prescrip-tion DMARD	Before conception			Pregnancy						One year after pregnancy	
						Trimester 1		Trimester 2		Trimester 3			
			Drugs prescribed	PDD	Days (N)	PDD	Days (N)	PDD	Days (N)	PDD	Days (N)	PDD	Days (N)
12	Inflam-matory bowel disease	5 months	SSZ	1.00	25	-	-	-	-	-	-	-	-
			AZA	0.67	400	-	-	-	-	-	-	-	-
			Mesalazine	2.65	729	2.66	100	-	-	2.66	200	2.66-	105
			Prednisolone	1.31	325	-	-	-	-	-	-	-	-
			Alendronic acid	1.00	285	-	-	-	-	-	-	-	-
			Paracetamol	0.50	10	-	-	-	-	-	-	-	-
13	Rheu-matic didease	5 months	SSZ	0.36	282	-	-	-	-	-	-	-	-
			MTX	0.32	595	-	-	-	-	-	-	-	-
			AZA	0.75	280	-	-	-	-	-	-	1.01	192
			Naproxen	2.00	675	-	-	-	-	-	-	2.00	150

* The daily dose was unknown in the database, the daily dose is assumed to be the average of the previous received prescriptions of this drug [1] O = Oral (Tablet), R = Rectal (enema) [2] co-medication used less then one week (7 days) are excluded, primary products (used for example for enema) are not taken into account

During pregnancy, anti-inflammatory and anti-rheumatic drugs were continued by two women, although they did not receive it in the third trimester. Corticosteroids, not prescribed before pregnancy, were prescribed to two women (20%) during pregnancy.

Combinations of DMARD (n=3)

Three women were dispensed a combination of SSZ, MTX or AZA before conception, SSZ was their initial DMARD (the end of table 3). Two women received MTX before conception, they both stopped it at least 5 months before pregnancy. None of the women receiving SSZ (N=3) or AZA (N=2) before conception, continued this during pregnancy. All women received co-medication before pregnancy, one women continued anti-inflammatory and anti-rheumatic drug during pregnancy but not during the third trimester.

Azathioprine (n=8)

Eight women were dispensed AZA before pregnancy as a single DMARD as can be seen in table 4. Six women (75%) were prescribed AZA during pregnancy, of them four women continued AZA throughout their whole pregnancy. All eight women were dispensed a corticosteroid for systemic use before pregnancy, two women continued these drugs during pregnancy. Seven women (88%) were dispensed an intestinal anti-inflammatory agent as well, they all continued this drug during and after pregnancy.

Guidelines

The FDA pregnancy risk categorization classifies MTX as X indicating that MTX should not be used during pregnancy[19]. In our database all women stopped MTX at least 5 months before conception. AZA and SSZ were both continued during pregnancy by some women. SSZ, classified as B by the FDA, is thought to be safe in pregnancy although teratogenic effects still can not be excluded[19;20].

Table 4. Dispensed DMARD and co-medication before, during and after pregnancy for women receiving an Azathioprine prescription as their initial DMARD before pregnancy

nr	Possible Indication	Last pres-cription DMARD	Before conception			Pregnancy						One year after pregnancy	
			Drugs prescribed[1]			Trimester 1		Trimester 2		Trimester 3			
				PDD	Days (N)	PDD	Days (N)	PDD	Days (N)	PDD	Days (N)	PDD	Days (N)
1	Inflam-matory bowel disease	-	AZA	0.58	365	0.67	100	-	-	0.67	200	0.67	300
			Mesalazine	0.99	737	2.00	100	1.99	67	1.99	67	1.99	134
			Prednisolone	1.00	500	1.00	100	1.00	100	-	-	0.74	91
			Paracetamol	-	-	-	-	-	-	-	-	0.44	30
2	Inflam-matroy bowel disease	-	AZA	0.60	1395	0.33	90	-	-	-	-	0.33	270
			Mesalazine O[1]	1.38	865	1.33	90	1.33	90	1.33	90	1.33	270
			Mesalazine R	2.00	555	-	-	-	-	-	-	-	-
			Prednisolone	4.00	140	-	-	-	-	-	-	-	-
			Etidronic acid and calcium	1.00	270	-	-	-	-	-	-	-	-

Nr	Possible indication	Last prescript-tion DMARD	Before concetption			Pregnancy						One year after pregnancy	
						Trimester 1		Trimester 2		Trimester 3			
			Drugs prescribed	PDD	Days (N)	PDD	Days (N)	PDD	Days (N)	PDD	Days (N)	PDD	Days (N)
3	Inflam-matory bowel disease	-	AZA	0.67	710	0.67	60	0.67	90	0.67	90	0.67	360
			Mesalazine O	2.00	707	-	-	2.00	90	2.00	90	2.00	300
			Prednisolone	1.27	130	-	-	-	-	-	-	-	-
			Prednisone	2.00	50	-	-	-	-	-	-	-	-
			Diclofenac R	1.54	13	-	-	-	-	-	-	2.00	3
			Diclofenac O	-	-	-	-	-	-	-	-	1.00	15
			Diclofenac IM	0.75	2	-	-	-	-	-	-	-	-
4	Inflam-matory bowel disease	-	AZA	064	825	0.50	90	0.50	90	0.75	180	1.00	270
			Mesalazine	1.50	360	-	-	1.00	90	1.00	180	0.50	370
			Loperamide	0.30	20	-	-	-	-	-	-	-	-
			Prednisolone	1.94	98	-	-	-	-	-	-	-	-
			Paracetamol/ Codeine	0.42	12	-	-	-	-	-	-	-	-
			Triticum	-	-	0.35	120	-	-	-	-	-	-

Nr	Possible indication	Last prescrip-tion DMARD	Before conception			Pregnancy						One year after pregnancy	
						Trimester 1		Trimester 2		Trimester 3			
			Drugs prescribed	PDD	Days (N)	PDD	Days (N)	PDD	Days (N)	PDD	Days (N)	PDD	Days (N)
5	Inflam-matory bowel disease	-	AZA	0.72	390	0.33	60	-	-	-	-	0.58	240
			Mesalazine	2.00	135	-	-	2.00	45	2.00	45	1.78	270
			Prednisolone	2.67	75	-	-	-	-	-	-	-	-
			Prednisone	-	-	-	-	-	-	-	-	2.38	80
			Alendronic acid	1.00	150	-	-	-	-	-	-	1.00	90
6	Inflam-matory bowel disease	-	AZA	1.00	287	1.00	63	1.00	66	1.00	33	1.00	260
			Mesalazine	1.60	310	161	63	162	66	161	33	161	252
			Prednisolone	1.03	329	0.87	77	0.75	80	0.75	40	1.31	252
			Paracetamol	0.30	50	0.50	10	-	-	-	-	-	-
			Paracetamol/ codeine	0.37	169	0.50	10	1.00	5	0.94	16	0.42	120
			Diclofenac	0.20	15	-	-	-	-	-	-	-	-

Nr	Possi-ble indication	Last prescrip tion DMARD	Before conception			Pregnancy						One ryear after pregnancy	
						Trimester 1		Trimester 2		Trimester 3			
			Drugs prescribed	PDD	Days (N)	PDD	Days (N)	PDD	Days (N)	PDD	Days (N)	PDD	Days (N)
6	Inflam-matroy bowel disease		Ibuprofen	1.15	24	-	-	-	-	-	-	-	-
			Ketopgofen	1.33	30	-	-	-	-	-	-	-	-
			Tramadol	0.50	130	-	-	-	-	-	-	-	-
			Etidronic acid and calcium	-	-	-	-	-	-	-	-	1.00	90
7	Inflam-matroy bowel disease		AZA	0.67*	280	-	-	-	-	-	-	-	-
			Meslazine	1.33*	550	1.33	100	1.33	100	1.33	100	1.33	100
			Prednisone	0.35*	230	-	-	-	-	-	-	-	-
			Paracetamol/ codeine	0.33	10	-	-	-	-	-	-	-	-
8	Inflam-matroy bowel disease		AZA	0.67	15	-	-	-	-	-	-	-	-
			Prednisolone	2.00	50	-	-	-	-	-	-	2.00	50
			Budesonide	-	-	-	-	-	-	-	-	1.00	33
			Mesalazine	-	-	-	-	-	-	-	-	1.33	50

Several studies found that AZA appears to be safe during pregnancy[20] although Norgard et al.[21] found an increased risk of malformations which could be confounded by disease activity. According to the FDA, AZA is classified as D, indicating that despite indications of foetal risks this drug can be considered during pregnancy if the benefits of therapy outweigh the potential risks. Anti-inflammatory and anti-rheumatic drugs were not used during the third trimester of pregnancy which is in agreement with the recommendations to withdraw these drugs 6 to 8 weeks before delivery[22]. Mesalazine (an intestinal anti-inflammatory agent)was continued during pregnancy by all women who also received it as co-medication before pregnancy, it is thought to be safe during pregnancy when given in conventional doses[23;24].

Discussion

Our study shows that DMARDs and related co-medication are received before, during and after pregnancy although no specific prescription patterns could be found. Azathioprine and sulfasalazine are continued during pregnancy by 60% (6/10) and 38% (5/13) of the women respectively, methotrexate was not continued during pregnancy.

Among the women to whom SSZ was dispensed as their initial DMARD (N=13), the most common prescribed co-medications before pregnancy are anti-inflammatory and anti-rheumatic drugs (69%, 9/13)) and analgesics (46%, 6/13). The most common prescribed drugs among women to whom AZA was dispensed as their initial DMARD (N=8) before pregnancy, were corticosteroids for systemic use (100%) and intestinal anti-inflammatory agents (88%). All women to whom an intestinal anti-inflammatory drug was dispensed before pregnancy continued this drug during pregnancy in contrast to other co-medications, which were mainly discontinued during the pregnancy period (table 7).

Table 5. Dispensed DMARD and co-medication before, during and after pregnancy for women receiving a methotrexate prescription as their initial DMARD before pregnancy

Nr	Possible indication	Last prescription DMARD	Before conception			Pregnancy						One year after pregnancy	
			Drugs prescribed	PDD	Days (N)	Trimester 1		Trimester 2		Trimester 3		PDD	Days (N)
						PDD	Days (N)	PDD	Days (N)	PDD	Days (N)		
1	?	6 months	MTX	5	1	-	-	-	-	-	-	-	-
2	Inflam-matroy bowel disease	33 months	MTX	1.51*	76	-	-	-	-	-	-	-	-
			Paracetamol	0.30	412	0.17	30	0.17	60	0.17	30	0.17	240
			Lactulose	-	-	-	-	-	-	-	-	0.20	150
3	?	5 months	MTX	7.50	20	-	-	-	-	-	-	-	-
4	?	8 months	MTX	0.95	76	-	-	-	-	-	-	-	-
			Lactulose	-	-	-	-	-	-	4.07	27	-	-

* The daily dose was unknown in the database; the assumed daily dose is the same as the daily dose from the other prescriptions 2 co-medication used less then one week (7 days) are excluded, primary products (used for example for enema) are not taken into account

Table 7. The number of women who received a drug from the class anti-inflammatory and anti-rheumatic drugs (M01A), analgesics and antipyretics (N02B), corticosteroids for systemic use (H02A) or intestinal anti-inflammatory agents (A07E)

>1 DMARD	*M01A*	*N02B*	*H02A*	*A07E*	*Other drugs **
Before pregnancy	2	1	1	1	N02AC04, M05BA04
During pregnancy	1	0	0	1	-
After pregnancy	2	0	0	1	N02AC04
SSZ	*M01A*	*N02B*	*H02A*	*A07E*	*Other drugs*
Before pregnancy	7	5	0	2	A06AC01
During pregnancy	2	1	2	2	-
After pregnancy	5	4	2	1	A07DA03
AZA	*M01A*	*N02B*	*H02A*	*A07E*	*Other drugs*
Before pregnancy	2	3	8	7	M05BB01, A07DA03, M05BA04, N02AX02
During pregnancy	0	1	2	7	A06AC07
After pregnancy	1	1	4	8	M05BA04, M05BB01
MTX	M01A	N02B	H02A	A07E	Other drugs
Before pregnancy	-	1	-	-	-
During pregnancy	-	1	-	-	A06AD11
After pregnancy	-	1	-	-	A06AD11

* N02AC04=Dextropropoxyphene, M05BA04=alendronic acid, A06AC01=Ispaghula (psylla seeds), A07DA03=loperamide, M05BB01=Etidronic acid and calcium, N02AX02=Tramadol, A06AC07=Triticum (wheat fibre) , A06AD11=Lactulose

In our database all women stopped MTX at least 5 months before conception which is according to the guidelines which state to wait at least one ovulatory cycle before attempting conception after discontinuation of methotrexate[4]. Withdrawal of anti-inflammatory and anti-rheumatic drugs 6-8 weeks before delivery[22] is described in the guidelines and was found in our data as well. Specific guidelines

on the use of AZA and SSZ could not be found although the FDA classification and several studies[19;20] indicate that it is safe to continue SSZ during pregnancy. Our data showed that SSZ was continued by approx. 38% of the women who used this drug before pregnancy. Most women, however, discontinued this drug during pregnancy, if this is related to disease activity, guidelines or other factors could not be determined.

Several studies found that AZA appears to be safe during pregnancy[20]. A recent case report by de Boer et al.[25] showed that the placenta forms a (relative) barrier to AZA and its metabolites and they plea that careful drug monitoring minimize intrauterine exposure to a metabolite of AZA. FDA classification indicate that despite indications of foetal risks this drug can be considered during pregnancy if the benefits of therapy outweigh the potential risks. Most women continued AZA (approx. 75%) during pregnancy, whether this is due to disease activity or other factors could not be determined although it seems likely that the disease activity plays an important role.

The strength of the pregnancy-IADB, a population based database, is that it can be used for detailed description of drug use patterns in general[10] or for individual patients or drugs.

To avoid interference of a previous pregnancy on drug prescribing only the first pregnancy of a woman registered in the database was included in the analysis.

Using this population-based prescription database bring about several limitations. It must be noted that, because of the design of this database, actual use of dispensed drugs could not be confirmed although Olesen et al.[26] showed that drugs prescribed for a chronic disease is almost always actually used by the women. We did not found any of the women receiving Tumor Necrosis Factor alfa (TNF-α) at some point before pregnancy, this is due to the Dutch health care system in which TNF-α is not dispensed through the regular community pharmacy of the women.

Indications are not available in the database, they were assigned by clinical pharmacists based on medication histories, but can not be confirmed due to the anonymous nature of the IADB. We did not find any consistency in the continuation or discontinuation of drugs during pregnancy and the indication of the patient. This

emphasize that the prescribing of drugs during pregnancy is based on the illness and characteristics of the individual patient.
For a child to show up in the database, a prescription had to be dispensed to the child, meaning that only live born children, to whom a prescription was dispensed, will be identified. Because information on the actual length of the gestation period was not available we used a standardized gestational period of 273 days (39 weeks) so misclassification of drug use can occur[7;9;27]. Administrative datasets with estimated gestation periods are useful in the research of drugs prescribing during pregnancy and misclassification should not considered being a major issue although it is essential to have precise data on drug exposure when exposure is related to pregnancy outcome[28].
Over the counter are not registered in the database and therefore the use of OTC-drugs is possible. Unpublished data from the EUROCAT-registration Northern-Netherlands showed that approx. 60% received a prescription for NSAIDs approx. 35% retrieved their NSAID OTC.
In conclusion, this study is the first describing azathioprine, sulfasalazine and methotrexate before, during and after pregnancy in detail. Administrative database, such as the pregnancy IADB, are useful in describing drug prescribing patterns for better understanding of drug use around time of conception and during pregnancy as well as after pregnancy in daily practice. In this data a specific prescribing pattern could not be found and we must conclude that the prescribing of a DMARD and related co-medication is based on the individual situation of the patient.

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Chapter 4

Drug utilization in pregnancy; the prescribing of disease modifying anti-rheumatic drugs in the GPRD.

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Summary

Medicine use in pregnancy involves weighing up benefits and risks of treatment to both the patient and the offspring. However, little is known about the potential risks of many drug treatments to the embryo or foetus. To evaluate safety in pregnancy, accurate knowledge regarding the timing of exposure in relation to embryogenesis is crucial.

Aims
This study investigated prescribing of disease modifying anti-rheumatic drugs (DMARDs) before and during pregnancy in UK general practice.

Methods
From the 585 280 pregnancies identified in the General Practice Research Database (GPRD), patients to whom a DMARD was prescribed at any time from four months before until the end of pregnancy were selected. All DMARD prescriptions were identified and timing of exposure was established for each patient, taking into account the amount and dosage prescribed as well as any switches and gaps in treatment. Alcohol consumption, smoking status, gestational age and age at time of delivery were estimated for all women; in addition, diagnoses and symptoms associated with DMARD prescribing were identified.

Results
A DMARD was prescribed just before or during 1100 pregnancies (814 deliveries, 286 terminations), mostly for malaria prophylaxis. Azathioprine, ciclosporin, (hydroxy)chloroquine and sulfasalazine were prescribed most often followed by methotrexate and leflunomide. Duration of exposure varied per product and pregnancy trimester. For most products, the frequency and duration of exposure increased in the second pregnancy trimester compared to the previous period.

Conclusions

To our knowledge this is the first study on a large scale to provide detailed insight into DMARD prescribing in pregnancy in UK general practice.

Introduction

Disease modifying anti-rheumatic drugs (DMARDs) are used in the treatment of rheumatic diseases such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). In addition, the same drugs are used in other inflammatory conditions such as ulcerative colitis and Crohn's disease and they can be prescribed for various other conditions such as other autoimmune diseases, malignancy, skin disorders including psoriasis or atopic dermatitis, or as malaria prophylaxis.1;2 When prescribing these products to women who are or intend to become pregnant, physicians have to weigh up benefits and risks of treatment to the patient and their offspring, while little is known about the risk they might pose to the embryo or foetus.

Some DMARDs are known or suspected to be teratogenic.[2,3] Leflunomide has been associated with prematurity and intrauterine growth retardation;[4] methotrexate has been associated with major malformations such as craniofacial and limb defects and central nervous system abnormalities.[5] The 'biologicals' are also classified as DMARDs. Thus far, 175 exposures to infliximab,[6-8] 62 exposures to etanercept,[6] and five exposures to adalimumab[6] have been described and to our knowledge none of these products have been associated with congenital malformations after exposure *in utero* in humans.[4,6,9] Exposure to etanercept and infliximab has been associated with prematurity and intrauterine growth retardation.[4]

About 100 pregnancies exposed *in utero* to penicillamine to treat Wilsons disease were summarized by Ostensen et al,[10] they concluded that approximately 5% of those exposed will have a congenital collagen defect. Congenital malformations seen after exposure to cyclophosphamide include facial anomalies, skin and musculoskeletal anomalies, visceral organ anomalies, growth retardation and possible developmental delays. Gold preparations have been associated with hydrocephaly, microphthalmia, limb defects and gastroschisis in animal studies[2] but not in humans. However, data in humans is very limited.[2,5,10]

Although often based on small numbers of exposed pregnancies in humans, some DMARDs are thought to pose a lower risk to the developing foetus then others:

data for 515 exposed pregnancies from the Swedish Medical Birth Registry as well as data from a nationwide case-control study with 17 exposed cases in Hungary have not identified an increased risk of major malformations after exposure *in utero* to sulfasalazine.[11,12] For azathioprine, two studies involving 46 pregnancies[13,14] have found no increased risk for congenital malformations and they concluded that this drug appears to be generally safe during pregnancy. In contrast, one study[15] found an odds ratio for malformations of 6.7 (CI 95% 1.4-32.4), which, according to the authors, may have been confounded by disease activity or the concurrent use of co-medications. In low doses chloroquine is considered to be generally safe,[2] however in animal studies embryotoxicity and teratogenicity have been reported after high doses of chloroquine. There is conflicting evidence for the potential of sensorineural deafness associated with chloroquine in rheumatic diseases.[16,17] Thus far, to our knowledge, hydroxychloroquine has not been associated with an increased risk of congenital malformations,[2,5,18] suggesting it may be safe to continue hydroxychloroquine throughout pregnancy.[5,18]. Bar Oz *et al* reviewed 15 studies involving 410 pregnant patients exposed to ciclosporin and concluded this product does not appear to be a major human teratogen.[19]

Given that the baseline frequency of major congenital malformations is around 3%[20] and given that exposure to DMARDs in pregnancy is unusual, assessing the effects of these products on the offspring is not straightforward. Most studies investigating such effects describe small exposed cohorts or case reports,[9] therefore statistical power of these studies is limited.

To carry out a systemic evaluation of safety of DMARD exposure *in utero,* accurate exposure assessment was necessary. Specifically, bearing in mind the process of embryogenesis, it was important to estimate the timing of exposure carefully. In addition, insight into co-prescribing and the morbidity patterns (which may carry their own increased risks of adverse pregnancy outcomes) of pregnant women using DMARDs was needed. In this study, we report on the prescribing of DMARDs to women in the UK before and during pregnancy using the General Practice Research Database (GPRD). In the companion paper[21] we report on a risk assessment study in the same population.

Method

Data source: GPRD

The GPRD comprises longitudinal data collected during the routine care of patients in general practice for between 4 and 6 % of the UK population. The information contained in the anonymous patient records include medical symptoms and diagnoses, drugs prescribed, smoking habits and alcohol use. However the completeness of these records varies: prescribing information is nearly complete whereas completeness of data on smoking and alcohol are incomplete and varies by practice. Practices are allocated an 'up to standard date' from which their data are deemed to be of a standard suitable for the purposes of research, based on the completeness of their data recording.22-25

Two versions of the GPRD are available: a closed dataset from EPIC VM (Epidemiology and Pharmacology Information Coral) in which data was collected until April 200226 and an MHRA dataset (Medicines and Healthcare products Regulatory Agency, Vision) for which data collection is ongoing.27 There is a considerable overlap between both databases. Merging both datasets was possible owing to cross-references provided by the MHRA.

Pregnancy determination

A cohort of pregnant women and their offspring were identified using data from the merged dataset. Similar to the procedure described by Hardy et al[28,29] for identifying pregnancies in the GPRD, all pregnancy markers were identified for every woman. Pregnancy start dates were estimated from the following data according to availability and in order of priority: expected date of delivery (EDD), last menstrual period (LMP), gestational age, default term for premature delivery (36 weeks) or default pregnancy term (40 weeks for delivery, 10 weeks for termination of pregnancy). Pregnancy end dates were logged by processing records in ascending date order within the following categories: delivery, termination of pregnancy (spontaneous or induced), and records of post-partum information. Pregnancy dates derived from successive events overlapping with a previously logged pregnancy were discarded for later review. Where sufficient evidence of pregnancy existed, the end date was estimated from the delivery and

post partum records. Pregnancies ending between 1st January 1992 and 29th March 2006 were determined for females aged 11-49 at the pregnancy start date. The registrations were verified and refined by comparing outcomes generated by the algorithm against individual patient records. For all delivered pregnancies a check was made for a possible linked birth, determined by a birth or registration record in the same family within 2 months of delivery. In cases where the mother was not the only woman with pregnancy records in the family in the selected period or when mothers were in residences with more than 20 residents, no attempts to link a birth were made. It was possible to establish dates for at least one pregnancy for 82.1% of the females who had at least one code relating to pregnancy and a possible link was made to a child's record for 79.7% of the delivered pregnancies.

Study population

For all women the last menstrual period (LMP) or first pregnancy marker associated with the pregnancy of interest had to occur at least 4 months after their registration date or practice up to standard date, whichever was later. The date of delivery or termination associated with the pregnancy of interest had to occur at least 3 months before the date of last data collection or date of leaving the practice whichever was earlier. Women who were permanently registered with their practice, aged 11-49 at the pregnancy start date and to whom a DMARD was prescribed at any time between three months before and three months after pregnancy were in principle eligible for analysis.

General population characteristics including age at end date of the pregnancy, pregnancy duration, alcohol use and smoking status were determined for all women.

Recording of smoking status and alcohol use is limited[22,23,25] and therefore information regarding such data specifically *during* pregnancy will not be available for every woman. Therefore alcohol consumption and smoking status during pregnancy were determined from a combination of data recorded during and before pregnancy. Priority was given to recording during pregnancy, however if this was unavailable then the last available record from before the pregnancy of interest was used. For each study participant we estimated the duration of DMARD

exposure before and during the first, second and third trimester of pregnancy as well as exposure throughout the entire pregnancy. Durations of episodes of use were calculated as the number of days for which the drug was prescribed continuously; this might include more than one prescription if no gaps between the prescriptions were recorded. Gaps of fewer than 7 days between two utilisation episodes were ignored and were considered part of continuous episode of drug exposure. Mean exposure time was defined as the total number of days of continuous exposure to a DMARD during a period (before pregnancy, first, second, or third trimester or entire pregnancy) divided by the number of all women exposed to the same product in the same period. Women who were exposed for one day or less or women for whom the date of exposure started at the same day as the end date of their pregnancy were excluded from the analysis. Concomitant drug use is possible, the period in which there is concomitant drug use will be counted for both drugs.

The indication for prescribing is not specified as such with the prescription record on the GPRD. However, one of the quality criteria is that the first time a drug is prescribed, the diagnosis or symptom for which the drug is prescribed needs to be recorded.[22] Therefore, for each DMARD in the study we investigated morbidity related to DMARD prescribing in the user population in an attempt to gain an understanding of the most common indications the DMARDs were prescribed for.

Results

From the 585 280 pregnancies identified, a total of 997 pregnancies were excluded. Reasons for exclusion were delivery date on January 1st 1992 (n=994), exposure for one day or less or date of exposure started at the same day as the end date of the pregnancy (n=3). From the pregnancies eligible for analysis, the number of pregnancies in which a DMARD was prescribed at some point three months before or during pregnancy can be seen in table 1. A record of DMARD prescribing was identified for 1100 out of 584 283 pregnancies (0.19%). In one per 1000 pregnancies a DMARD was prescribed before pregnancy (0.13% (784/584 283); 95% CI 0.12-0.14).

Table 1. Population characteristics of women and their pregnancies exposed to a DMARD from three months leading up to and during pregnancy and a pregnant reference group available from the GPRD.

	DMARD exposed	Reference group	P-value
Number of pregnancies (%)	1100 (0.2)	583 183 (99.8)	
Number of women (%)	981 (0.3)	392243 (99.7)	
Age (Mean, ±SD)	30.8 (5.7)	29.0 (6.2)	t = 0.000
Age category (N, %)			X^2 = 0.000 X^2_{trend} = 0.000
11-14	0 (0.0)	490 (0.1)	
15-19	24 (2.2)	42394 (7.3)	
20-24	136 (12.4)	102505 (17.6)	
25-29	290 (26.4)	158995 (27.3)	
30-34	365 (33.2)	167203 (28.7)	
35-39	213 (19.4)	87061 (14.9)	
40-44	62 (5.6)	22344 (3.8)	
45+	10 (0.9)	2191 (0.4)	
Deliveries (N, %)	814 (74.0)	413972 (71.0)	X^2 = 0.028
Terminations (N, %)	286 (26.0)	169211 (29.0)	
Gestational age (deliveries)			
Duration (days, mean ±SD)	276.7 (12.7)	278.5 (10.4)	t = 0.000
Term (>37 weeks) (N, %)	762 (93.6)	397357 (96.0)	X^2 = 0.001
Premature (34 to 37 weeks) (N, %)	37 (4.5)	12929 (3.1)	
Very premature (<34 weeks)	15 (1.8)	3686 (0.9)	
Gestational age (terminations)			
First trimester	278 (97.2)	165206 (97.6)	X^2 = 0.632

	DMARD exposed	Reference group	P-value
(N,%)			
Second trimester (N,%)	8 (2.8)	4005 (2.4)	
Alcohol use (N, %)^			$X^2 = 0.101$ $X^2_{trend} = 0.182$
Unknown	504 (45.8)	278892 (47.8)	
Teetotal	148 (13.5)	70505 (12.1)	
Low to moderate alcohol use (1-2 units/day)	412 (37.5)	219860 (37.7)	
Heavy alcohol use and alcohol abuse (>2 units/day)	36 (3.3)	13926 (2.5)	
Smoking (N, %)^			$X^2 = 0.179$ $X^2_{trend} = 0.734$
Unknown	363 (33.0)	193743 (33.2)	
Non-smoker	446 (60.5)	222564 (57.1)	
Smoker	291 (39.5)	166876 (42.9)	

* Deliveries only

^ Smoking habits and alcohol consumption during pregnancy was recorded for only 15% and 10% of the women respectively. Therefore, when these records were not available during pregnancy, the last available record before the pregnancy of interest was used.

The same was seen during pregnancy (0.14% (837/584 283); 95% CI 0.13-0.15). Women exposed to a DMARD were significantly older (p=0.000) and had a marginally shorter pregnancy duration (p=0.000) than women in the reference group. Premature (4.5%) and very premature (1.8%) births occurred significantly more often among women exposed to a DMARD (p=0.001). Recording of alcohol consumption and smoking status was very limited *during* pregnancy (although it was more complete when additional data from before the pregnancies was used): information regarding alcohol consumption *during* pregnancy was available in 10% and smoking status in 15% of all pregnancies. After supplementing this with recording from before pregnancy, no differences were observed between DMARD

users and non-users in terms of alcohol consumption (p=0.101) and smoking habits (p=0.179). Table 2 suggests that the majority of the women received a DMARD for malaria prophylaxis. For 3.2% of the women no diagnoses or symptoms were recorded that provided potential explanations or reasons for DMARD prescribing.

Table 2. Morbidities related to DMARD prescribing among pregnant women (n=748)

Morbidity (N, %)	
Rheumatic diseases[#]	170 (22.5)
(Rheumatoid) arthritis	90
Systemic/discoid) lupus erythematosus	58
Psoriatic arthropathy	15
Alkylosing spondylitis	1
Other	9
Inflammatory bowel diseases	216 (28.6)
Crohn's disease	103
(Ulcerative) colitis	104
Other	9
Transplantations	43 (5.7)
Kidney	28
Liver	10
Other	5
Malaria prophylaxis	267 (35.4)
Skin conditions (including psoriasis, eczema)	8 (1.1)
Hepatitis	10 (1.3)
Myasthenia gravis	3 (0.4)
Other	14 (1.9)

Categories are not mutually exclusive

Drug exposure

Table 3 shows the number of pregnancies receiving a certain DMARD.Table 4 shows the mean exposure time to DMARDS prescribed in the three months leading up to and during pregnancy. Aurofin (oral gold preparation) and infliximab

were prescribed before but not during pregnancy; both drugs were prescribed for short periods of time. The mean exposure time to azathioprine, ciclosporin, hydroxychloroquine, leflunomide, methotrexate and sulfasalazine before pregnancy was higher when compared to the mean exposure in the first trimester of pregnancy. With the exception of leflunomide, the same was observed when exposure during the first trimester was compared with the second trimester. For all products, the mean duration of exposure decreased in the third trimester.
The mean exposure time to chloroquine was approximately the same before and in the first trimester of pregnancy, in the second trimester an increase was seen and in the third trimester a decrease was observed. Compared with duration of use before pregnancy, prescribing of penicillamine and sodium thiomalate decreased in the first trimester. Finally, penicillamine prescribing also decreased as pregnancies progressed.

Table 3. Number of pregnancies (women) in which DMARDs were prescribed before or during pregnancy (n=1100)

	Number of pregnancies (women) exposed to a DMARD				
	Before pregnancy	Trimester 1	Trimester 2	Trimester 3	Entire pregnancy
Azathioprine	212 (177)	194 (163)	119 (105)	103 (88)	212 (199)
Chloroquine	217 (214	128 (128)	51 (51)	10 (10)	189 (189)
Ciclosporin	62 (50)	55 (44)	32 (27)	35 (28)	60 (52)
Hydroxychloroquine	64 (60)	39 (37)	16 (15)	19 (18)	47 (45)
Infliximab	1 (1)	-	-	-	-
Leflunomide	3 (3)	4 (4)	1 (1)	-	4 (4)
Methotrexate	19 (19)	15 (14)	2 (2)	2 (2)	16 (16)
Penicillamine	10 (10)	12 (12)	2 (2)	3 (3)	14 (14)
Sulfasalazine	237 (204)	180 (152)	91 (81)	93 (80)	217 (198)
Sodium Thiomalate	3 (3)	1 (1)	-	-	1 (1)
Any DMARD	784 (694)	580 (510)	289 (260)	241 (209)	836 (748)

Chloroquine, often prescribed for a shorter period of time and in a lower dose for malaria prophylaxis,[1] was prescribed in the first trimester of pregnancy of 128

pregnancies. In 95.3 % of these pregnancies chloroquine had been prescribed for malaria prophylaxis; other reasons were rheumatic disease (4 times) or unknown (twice). None of the women receiving chloroquine for their rheumatic disease continued to be prescribed this drug in the second or third trimester. The majority of women received hydroxychloroquine for a rheumatic disease, none of the women appeared to have been prescribed it for malaria prophylaxis. Among the women to whom a DMARD was prescribed, in 237 pregnancies the women received sulfasalazine in the three months leading up to their pregnancy (237/1100, 30.2%) In 146 pregnancies the women continued to receive sulfasalazine during pregnancy (146/237, 61.6%). Azathioprine was prescribed in the three months leading up to the pregnancy in 212 pregnancies (212/1100, 27.0%) and continued in 185 pregnancies during pregnancy (82.5%).

Table 4. Mean exposure time^ in days to a DMARD before and during pregnancy

	Before	Trimester 1	Trimester 2	Trimester 3	Entire pregnancy
	Number of days, mean (range)				Days, mean (±SD)
Azathioprine	58.4 (1-91)	69.6 (1-91)	89.4 (1-112)	64.1 (1-84)	144.0 (13.3)
Chloroquine	39.9 (1-85)	39.7(1-91)	57.2 (5-97)	52.9 (5-73)	44.4 (9.1)
Ciclosporin	61.8 (1-91)	78.9 (1-91)	100.2 (1-112)	64.0 (1-82)	162.1 (18.2)
Hydroxychloroquine	48.1 (1-91)	65.2 (1-91)	84.9 (2-112)	54.3 (1-81)	102.4 (15.5)
Infliximab	1.0 (1)	-	-	-	-
Leflunomide	59.3 (10-64)	72.0 (31-80)	63.0 (63)	-	87.8 (6.4)
Methotrexate	46.1 (2-71)	45.7 (2-71)	51.5 (2-88)	30.0 (2-49)	53.0 (11.1)
Penicillamine	51.5 (11-71)	49.6 (1-89)	73.0 (21-60)	25.0 (1-46)	58.3 (24.0)
Sulfasalazine	46.6 (1-91)	56.2 (1-91)	76.0 (1-112)	51.1 (1-91)	97.6 (13.2)
Sodium Thiomalate	14.0 (8-15)	7.0	-	-	-

^Mean exposure time: total number of days of continuous exposure to a DMARD (calculated from number of days the drug was prescribed for continuously) during the period (before pregnancy, first, second, or third trimester or entire pregnancy) divided by the number of pregnancies exposed to the drug in that period (table 1).

Discussion

In the UK 1 per 1000 women received a DMARD during pregnancy. With respect to sulfasalazine and azathioprine it was seen that the majority of the women prescribed these products in the three months leading up to pregnancy continued to have them prescribed during pregnancy. Products such as methotrexate, leflunomide, penicillamine, hydroxychloroquine and chloroquine were mainly stopped during the first trimester of pregnancy.

According to UK guidelines it is essential to take effective contraception during treatment and for at least 2 years after treatment for leflunomide.[1] Drugs such as methotrexate, penicillamine, cyclophosphamide, anakinra, etanercept, adalimumab, and infliximab need to be avoided during pregnancy and contraceptive measures have to be in place for at least three months or longer after the last dose for many of these products. Unplanned pregnancies might explain why these drugs were continued by some women, but it might also be possible that the severity of the disease lead the physician to prescribe these drugs, even in pregnancy. Manual review of the exposed women's computerised medical records using the coding browser we developed in house did not provide sufficient insight into the proportion of these pregnancies that was unplanned.

From this study, it becomes apparent that in the UK methotrexate is being prescribed during pregnancy. This is in contrast with data from the Netherlands,[30] where guidelines with respect to methotrexate use in pregnancy are the same as in the UK.[1,31] This difference may be partly explained by the higher proportion of unplanned pregnancies in the UK (33%,[32]) compared with the Netherlands (8-24%,[33]).

Among the women receiving a DMARD before or during pregnancy the percentages of pregnancies in which sulfasalazine and azathioprine were prescribed before pregnancy was comparable; 30% (UK) and 37% (NL) for sulfasalazine and 27% and 29% for azathioprine. However, the percentage of women continuing these drugs during pregnancy differed; 62% (UK) and 38% (NL) for sulfasalazine and 83% (UK) and 60% (NL) for azathioprine. Perhaps cultural

differences in countries with respect to medication use in pregnancy might partly explain the observed differences between the two countries. De Vigan et al[34] compared medication use amongst pregnant women using data from EUROCAT registration in four countries. And although the study population is different, they found that in general, medication use was lower in the UK than in the Netherlands. Another explanation for the observed effect might be found in the differences in databases. The IADB.nl used in the Netherlands only contains pregnancies resulting in live births, while the GPRD also contains records of pregnancy terminations.

Chloroquine can be considered as medication taken for occasional use[35] and is mostly discontinued as soon as pregnancy is discovered. Since most women find out that they are pregnant during the first trimester of pregnancy, a decrease of pregnancies in which chloroquine is prescribed after the first trimester was to be expected. In our study, most women prescribed chloroquine during pregnancy appeared to have been prescribed this product for malaria prophylaxis. Guidelines state that under certain circumstances, chloroquine and hydroxychloroquine can be continued during pregnancy in a rheumatic disease[1] although most women will experience an improvement of symptoms during pregnancy.[10] None of the women (n=4) with a rheumatic disease continued chloroquine after the first trimester of pregnancy. With respect to hydroxychloroquine, a decrease in the number of women receiving hydroxychloroquine during pregnancy was seen, while the mean duration of use increased in the different trimesters as pregnancy progressed.

This drug utilisation study was set up to gain an understanding of / obtain insight into the extent of exposure *in utero* to DMARDs as well as the morbidity patterns of the mothers. The majority of women received their DMARD for malaria prophylaxis. Women also received these drugs for rheumatic diseases and inflammatory bowel disease, which was to be expected since many DMARDs are licensed for these indications. The process of determination of co-morbidities has been time consuming but is extremely important if the underlying disease can be a confounding factor in risk assessment studies.

The GPRD is very useful in drug utilisation research and provides detailed information on prescribing, including the products prescribed as well as the prescribed dosage and duration of use. In the development of congenital malformations the timing of exposure is crucial;[2] detailed information on when the drug was taken is therefore essential. For other pregnancy outcomes such as premature birth, exposure during second or third trimester may be relevant. Because no information is available regarding actual medication use, this exposure assessment is limited by lacking information regarding non-adherence. However, in their investigation of medication use in pregnancy, Olesen *et al* found that for chronic conditions most prescribed medication was actually taken by pregnant women (as determined by self-reporting by these women).[36] Since with the exception of chloroquine, DMARDs are usually prescribed for chronic diseases, we would argue that it is not unreasonable to assume this medication will have been used if a prescription was issued. The use of DMARDs in the three months leading up to pregnancy was used to describe DMARD use before pregnancy. It can be assumed that a woman using a DMARD will try to stop their medication if possible. It then might be possible that DMARD use before pregnancy was even higher as being described in this study.

Conclusion

DMARDs were prescribed before and during pregnancy in the UK although not always in accordance with national prescribing guidelines. DMARDs were prescribed for different indications including rheumatic and inflammatory bowel diseases. The prescribing of DMARDs around pregnancy decreased; this may be partly owing to guidelines being followed but also owing to the uncertainty of DMARD safety during pregnancy. The detailed information on exposure to DMARDs described in this study can be used to evaluate any associations between DMARD exposure and selected birth outcomes.

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Chapter 5

DMARDs in pregnancy; birth outcomes after prescribing DMARDs using the GPRD

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Summary

Background and objectives

For many DMARDs there is a lack of properly conducted controlled risk assessment studies in humans and recommendations towards their use in pregnancy are often based on animal data or small exposed cohorts. This study aims to evaluate risks associated with the use of DMARDs during pregnancy in relation to preterm birth and congenital anomalies using the General Practice Research Database (GPRD).

Methods

A cohort study was conducted. From the GPRD, all pregnancies between 1 January 1992 and 26 March 2006 were identified and pregnancy outcome, gestational age, alcohol use and smoking habits were determined. Among these pregnancies, DMARD prescribing in the three months leading up to pregnancy and in the first, second or third trimester of pregnancy was determined. Associations between DMARD use and preterm birth (<37 weeks) and birth defects were calculated using unconditional logistic regression. Two comparator groups were used: 1) those from the general population not prescribed DMARDs during pregnancy and 2) those prescribed sulfasalazine.

Results

We did not identify an increased risk of pregnancy termination or congenital malformations associated with DMARD prescribing during the first trimester. Azathioprine use in the second trimester was associated with an increased risk of preterm birth when compared with women not prescribed a DMARD at all (OR 3.25 (1.82,5.78).

Discussion

Some of the indications for which DMARDs are prescribed carry an increased risk of prematurity. The associations found, therefore, may reflect a risk from the medications prescribed or they may reflect risks associated with the study population’s morbidity. The fact that no increase in terminations and no increased

risk of malformations were found is reassuring for women who are exposed to DMARDs whilst pregnant.

Conclusions

This study suggests azathioprine, if prescribed during pregnancy, may increase the risk of premature birth although the possibility of confounding by indication cannot be ruled out. The study has not identified any major increase in congenital malformations.

Background

In rheumatoid arthritis and systemic lupus erythematosus drug use during pregnancy is sometimes unavoidable. Potential teratogenic effects of a drug will influence the decision whether to discontinue or continue drugs such as disease modifying anti-rheumatic drugs (DMARDs) during pregnancy. Methotrexate, often used in rheumatic and other autoimmune diseases, is considered to be teratogenic. (1;2) Exposure in utero to methotrexate has been associated with an increased risk of congenital malformations such as craniofacial and limb defects, central nervous system abnormalities, and myelosuppression (3). In relation to birth outcomes methotrexate is known for its abortifacient properties; an increased risk of preterm births has also been reported although this may have been associated with the disease for which the drug was being prescribed (4). Sulfasalazine crosses the placenta (2;3) but thus far it does not appear to increase the risk of foetal abnormalities or spontaneous abortions (3;5). Azathioprine was found to be teratogenic in rabbits (2); in humans the foetus lacks the enzyme that converts azathioprine into its active metabolites and this way it seems to be protected from teratogenic effects (3). Adverse effects seen after exposure to azathioprine throughout pregnancy include foetal growth retardation and chromosomal abnormalities (3). The use of azathioprine has also been associated with an increased frequency of preterm births and low birth weight (6;7). Cyclosporine showed embryo and foetal toxicity in rats and rabbits but thus far, teratogenic effects in human have not been observed (2). In human, a increased rate of prematurity was seen, a increased risk of congenital malformations was not found (2;8). A potential problem for women using cyclosporine is foetal growth retardation but this problem is probably related to the mother's disease rather then to the drug use (2). Leflunomide exhibits dose-related teratogenicity in animals, therefore it is contraindicated in pregnancy (2). For instance, animal studies in rats and rabbits showed malformations of the head, rump, vertebral column, ribs and limbs (9). Data on the use of leflunomide in humans is limited and the risk of congenital malformations cannot be determined (2). After the use of high doses of chloroquine, studies in rats showed skeletal and ocular defects. Similar data for the closely related agent hydroxychloroquine are not available (2;3). In humans, data

on hydroxychloroquine is scarce, but from the data available it does not seem to pose a significant risk to the foetus. Retinal or ototoxicity was not seen and at low doses the agent has not shown to be harmful to the foetus. In higher doses, as being used in SLE or RA, a risk is probable but the magnitude of this increase is unknown (2). Chloroquine is not considered to be a major teratogen in human although a small increase in the risk of birth defects cannot be excluded (2).
Tumor necrosis factor alfa drugs (TNFα) did not show embryo toxicity or teratogenicity in animal studies (2;3;10), in humans data is scarce but up to now they have not been associated with embryo toxicity, teratogenicity or pregnancy loss (10).
Gold preparations showed teratogenicity in animal studies, experience in humans is limited but have not identified a major teratogenic risk (2;3). Penicillamine showed teratogenicity in animal studies; in humans exposure resulted in serious disorders of connective tissue (3).
For many drugs there is a lack of proper conducted controlled studies in human and recommendations towards its use in pregnancy are often based on animal data or small exposed cohorts (2;11-15). This study aims to evaluate risks associated with the use of DMARDs during pregnancy in relation to preterm birth and congenital anomalies.

Method

Previously it was shown that the GPRD can be used to identify drugs use among a pregnant patient population. (16-18) After identification of the use of DMARDs before and during pregnancy, we used the GPRD to evaluate risks associated with the use of these DMARDs.

Pregnancy determination

A cohort of pregnant women and their offspring were identified from the GPRD from 1 January 1992 to 26 March 2006. Similar to the procedure described by Hardy et al. (16;17) for identifying pregnancies in the GPRD, all pregnancy markers as well as all available pregnancy outcomes were identified for every woman. Pregnancy start dates were estimated from the following data according to

availability and in order of priority; expected date of delivery (EDD), last menstrual period (LMP), gestational age, default term for premature delivery (36 weeks) or default pregnancy term (40 weeks for delivery, 10 weeks for termination of pregnancy). Pregnancy end dates were logged by processing records in ascending date order within the following categories: delivery, termination of pregnancy (including miscarriages), and post-partum. Pregnancy dates derived from successive events overlapping with a previously logged pregnancy were discarded for later review. Where sufficient evidence of pregnancy existed the end date was estimated from the delivery and post partum records. Pregnancies ending between 1st January 1992 to 29th March 2006 were determined for valid females who were aged 11-49 at the pregnancy end date. The registrations were validated and refined by comparing outcomes generated by the algorithm against individual patient records. For all delivered pregnancies a check was made for a possible linked birth, determined by a birth or registration record in the same family within 2 months of delivery. In cases where the mother was not the only woman with pregnancy records in the family in the selected period or when mothers were in residences with more than 20 residents, no attempts to link a birth were made. It was possible to establish dates for at least one pregnancy for 82.1% of the females who had at least one code relating to pregnancy and a possible link was made to a child's record for 79.7% of the delivered pregnancies.

Study population

For all women in the cohort the last menstrual period (LMP) or first pregnancy marker associated with the pregnancy of interest had to occur at least 4 months after their registration date or practice up to standard date, whichever was later. The date of delivery or termination, associated with the pregnancy of interest, had to occur at least 3 months before the date of last data collection or date of leaving the practice whichever was earlier. All women who were permanently registered with their practice and aged 11-49 at the pregnancy end-date were eligible for analysis. General population characteristics, including age at end date of the pregnancy, pregnancy duration, alcohol use and smoking habits, were determined for all women.

Data recording on smoking and alcohol use is often incomplete (19-21) so it can be expected that data during pregnancy will not be available for every woman. Therefore the alcohol consumption and smoking habits during pregnancy were determined if available. In case there were no records on alcohol or smoking available during pregnancy, the last available record from before the pregnancy of interest was used. Women to whom a DMARD was prescribed at any time between three months before and three months after pregnancy were identified. For those, the timing of prescribing was classified as being in the three months leading up to pregnancy or during the first, second or third pregnancy trimester.

Statistical analysis

Pearson Chi-squared test (for differences in proportions) or student t-test (for differences in means) was used to test differences between the general population characteristics (SPSS 12.0.1). The association between DMARDs prescribed in the second and third trimester of pregnancy and the pregnancy outcomes premature birth and terminations was estimated using unconditional logistic regression analysis. To investigate this associations, the association was first tested among women who were not prescribed a DMARD as a comparison group. Secondly, the group of women using sulfasalazine was used as a reference group. DMARD use and the association with various congenital malformations were estimated as well to generate hypothesis about DMARD use and congenital malformations. This association was tested among a group of women using sulfasalazine as a reference group. Covariates considered for inclusion in the regression models as potential confounders were alcohol use, smoking habits, age of the mother at time of delivery and folic acid use in before and during the first trimester of pregnancy (only known in the women using a DMARD). The analyses were conducted in STATA 9.0 (StataCorp LP, College Station, TX, USA)

Results

Population

In the GPRD 585 280 pregnancies were identified; 997 pregnancies were excluded because their delivery date was January 1st 1992 (n=994) exactly and exposure to

a DMARD was one day or less or the date of exposure started at the same day as the end date of the pregnancy (n=3). From the pregnancies eligible for analysis 0.19% of the women (n=1100) were prescribed a DMARD before or during pregnancy. Women to whom a DMARD was prescribed during pregnancy were significantly older (30.8±5.7 vs. 29.0±6.2 years of age; p=0.000) and had a marginally shorter gestational period (276.7±12.7 vs. 278.5±10.4 days; p=0.000). Termination of pregnancy occurred more often in pregnancies not exposed to DMARDs *in utero* (29.0% non-exposed vs. 21.3% exposed; p=0.000). The women did not differ with respect to alcohol use and smoking habits (table 1).

Birth outcomes: gestational age

Women who received a prescription for a DMARD three months leading up to the pregnancy and during pregnancy delivered a very premature (<34 weeks) or premature child (between 34 and 37 weeks) more often than women without having prescribed a DMARD (table 1). Preterm birth occurred significantly more frequently among women using azathioprine in the second trimester (OR 3.25 (1.82,5.78)) when compared to women not exposed to a DMARD. An increase, although not significant, was also seen when the women using azathioprine during the second trimester were compared with women using sulfasalazine. Furthermore it was noted that among women, using hydroxychloroquine in the second and trimester of pregnancy, prematurity occurred more often in comparison with the women not exposed or exposed to sulfasalazine. However, none of these associations was significant (table 2).

Birth outcomes: birth defects

The following birth defects were found amongst the exposed study population: heart defects (including heart murmurs and ventrical septal defects), patent ductus arterious, defects of the eye, skull, foot, and central nervous system, anal stenosis, genitourinary defects (including hypospadias and undescended testis), hernia and other unspecified birth defects. Exposure to a DMARD in relation to these birth defects was investigated in a hypothesis generating manner. Women prescribed a DMARD were compared with women to whom sulfasalazine was prescribed during pregnancy, none of the associations investigated was found to be significant. Table

3 presents a selection (approx. 25%) of the associations investigated. For most birth defects, such as patent ductus arterious and defects of the central nervous system, numbers were to low to investigate the association. Drug exposure to methotrexate, penicillamin, leflunomide, and the gold preparations is also to low to investigate any associations. High point estimates were noted for hernia and azathioprine, ciclsporin and hydroxychloroquine, but also large confidence intervals were seen.

Table 1. Population characteristics of all patients

	DMARD exposed	Reference group	
Pregnancies (N,%)	1100 (0.19)	583 183 (99.8)	
Before pregnancy (N,%)	784 (0.13)	583 499 (99.9)	
During pregnancy (N,%)	836 (0.14)	583 447 (99.9)	
Women (N,%)	981 (0.25)	392 243 (99.7)	
Before pregnancy (N,%)	694 (0.18)	392 427(99.8)	
During pregnancy (N,%)	748 (0.19)	392 375 (99.8)	
Characteristics for pregnancies in which a DMARD was prescribed during pregnancy			
	836 pregnancies	583 447 pregnancies	
	DMARD exposed	Reference group	P-value
Age (Mean, ±SD)	30.9 (5.8)	29.0 (6.2)	0.000
Age category			$X^2 = 0.000$ $X^2_{trend} = 0.000$
11-14	0 (0.0)	490 (0.1)	
15-19	19 (2.3)	42388 (7.3)	
20-24	105 (12.6)	102536 (17.6)	
25-29	216 (25.8)	159069 (27.3)	
30-34	271 (32.4)	167297 (28.7)	
35-39	166 (19.9)	87108 (14.9)	
40-44	51 (6.1)	22355 (3.8)	

45+	8 (1.0)	2193 (0.4)	
Terminations (N,%)	178 (21.3)	169 319 (29.0)	0.000
Deliveries (N,%)	658 (78.7)	414 128 (71.0)	
Gestational age (deliveries)			
Duration (days, mean, ±SD)*	278.5 (10.4)	276.6 (13.0)	0.000
Term (>37 weeks)	615 (93.5)	397 594 (96.0)	0.001
Premature (34 to 37 weeks)	29 (4.4)	12937 (3.1)	
Very premature (<34 weeks)	14 (2.1)	3687 (0.9)	
Gestational age (terminations)			
First trimester terminations	172 (96.6)	165 312 (97.6)	0.378
Second trimester terminations	6 (3.4)	4007 (2.4)	
Alcohol use (N, %)			$X^2 = 0.401$ $X^2_{trend} = 0.548$
Unknown	390 (46.7)	279 006 (47.8)	
Teetotal	109 (13.0)	70 544 (12.1)	
Low to moderate alcohol use (1-2 units/day)	312 (37.3)	219 960 (37.7)	
Heavy alcohol use and alcohol abuse (>2 units/day)	25 (3.0)	13 937 (2.4)	
Smoking (N, %)			$X^2 = 0.079$ $X^2_{trend} = 0.537$
Unknown	271 (32.4)	193 835 (33.3)	
Non smoker (N, %)	344 (41.1)	222 666 (38.2)	
Smoker (N, %)	221 (26.4)	166 946 (28.6)	

*deliveries only

Birth outcomes: gestational age

Women who received a prescription for a DMARD delivered a very premature (<34 weeks) or premature child (between 34 and 37 weeks) more often than women without having prescribed a DMARD (table 1). Preterm birth occurred significantly

more among women using azathioprine (OR 4.13 (2.49-6.85)), hydroxychloroquine (OR 4.53 (1.58-13.02)), leflunomide (OR 12.93 (1.18-140.87)) and sulfasalazine (OR 2.23 (1.17-4.27)) during the first trimester of pregnancy when compared to women not using a DMARD at all. In the second trimester the same was seen for the use of azathioprine, hydroxychloroquine, and sulfasalazine. When compared with women using a DMARD other than the DMARD of interest the use of azathioprine during the first (OR(adj) 2.96 (1.56-5.61)) and second (OR(adj) 2.74 (1.38-5.43)) trimester of pregnancy was significantly associated with preterm birth.

Table 2a. Risk of premature birth (GA<37 weeks) associated with DMARD prescribing during pregnancy compared with the general population as the reference category.

Exposure to a DMARD	Trimester		<37 weeks	>37 weeks	Unadjusted OR (CI 95%)	Adjusted OR (CI 95%)#
Azathioprine	Second	-	15,228	399,440	3.25 (1.82,5.78)*	3.17 (1.77,5.65)*
		+	13	105		
	Third	-	15,238	399,448	0.81 (0.26,2.56)	0.80 (0.25,2.53)
		+	3	97		
Cyclosporin	Second	-	15,238	399,516	2.71 (0.83,8.90)	2.68 (0.83,8.69)
		+	3	29		
	Third	-	15,239	399,515	1.75 (0.42,7.31)	1.74 (0.42,7.20)
		+	2	30		
Hydroxy-chloroquine	Second	-	15,239	399,531	3.74 (0.85,16.48)	3.49 (0.80,15.32)
		+	2	14		
	Third	-	15,239	399,528	3.08 (0.71,13.35)	2.88 (0.67,12.44)
		+	2	17		
Sulfasalazine	Second	-	15,235	399,460	1.85 (0.81,4.24)	1.81(0.79,4.14)
		+	6	85		
	Third	-	15,237	399,457	1.19 (0.44,3.25)	1.19 (0.44,3.25)
		+	4	88		

* significant

\# OR is adjusted for alcohol use and smoking habits and age (older or younger then 35 years of age)

Table 2b. Risk of premature birth (GA<37 weeks) associated with DMARD prescribing during pregnancy compared within the group of DMARD users, *using sulfasalazine* as the reference category.

DMARD	Trimester		<37 weeks	>37 weeks	Unadjusted OR (CI 95%)	Adjusted OR (CI 95%)#
Azathioprine	Seccond	-	9	7	2.16 (0.89,5.24)	2.16 (0.89,5.24)
		+	13	105		
	Third	-	9	157	0.54 (0.14,2.05)	0.49 (0.13,1.87)
		+	3	97		
Cyclosporin	Second	-	9	160	1.84 (0.47,7.23)	2.12 (0.50,8.98)
		+	3	29		
	Third	-	9	160	1.18 (0.24,5.78)	1.16 (0.22,5.94)
		+	2	30		
Hydroxy-chloroquine	Second	-	9	160	2.54 (0.50,12.97)	2.49 (0.44,14.19)
		+	2	14		
	Third	-	9	159	2.08 (0.41,10.46)	1.87 (0.33,10.58)
		+	2	17		

OR is adjusted for alcohol use and smoking habits and age (older or younger then 35 years of age)

Birth outcomes: birth defects

All DMARDs (n=11) were tested against the following birth defects: heart defects (including heart murmurs and ventrical septal defects), patent ductus arterious, defects of the eye, skull, foot, and central nervous system, anal stenosis, genitourinary defects (including hypospadias and undescended testis), hypospadias, hernia and other as well as any birth defect (n=12). Associations between birth defects in general and DMARDs were not found (table 3). First trimester use of sulfasalazine was associated with genitourinary defects (OR(crude) 3.51 (1.22-10.02)) and first trimester use of leflunomide was associated with hernia (OR(crude) 32.46 (2.76-381.22). When adjusted for alcohol, smoking, age and folic acid the odds increased to 4.99 (1.56-15.93) and 53.08 (4.30-655.71), receptively. None of the other drugs was associated with any specific birth defect.

Table 3. Association between first trimester DMARD prescribing to mothers who delivered a live born (n=658) or had a termination (n=178) and congenital malformation compared to mothers to whom sulfasalazine was prescribed as determined by unconditional logistic regression.

Congenital malformation		DMARD		OR (95% CI)
		Azathioprine		
		-	+	
Heart	-	123	129	0.79 (0.23,2.68)
	+	6	5	Adjusted 0.86 (0.24,3.14)
Eye	-	126	131	0.96 (0.18,4.87)
	+	3	3	
Genitourinary	-	123	133	0.15 (0.02,1.30)
	+	6	1	
Hernia	-	128	129	4.96 (0.57,43.23)
	+	1	5	
Any*	-	103	110	0.86 (0.47,1.60)
	+	26	24	Adjusted 0.91 (0.48,1.72)
Termination	-	47	60	0.81 (0.52,1.27)
	+	129	134	Adjusted 0.86 (0.54,1.39)
		Cyclosporin		
		-	+	
Heart	-	127	34	1.24 (0.24,6.49)
	+	6	2	
Eye	-	130	34	2.55 (0.41,15.95)

Congenital malformation		DMARD		OR (95% CI)
	+	3	2	
Genitourinary	-	127	36	-
	+	6	0	
Hernia	-	132	34	7.76 (0.68,88.83)
	+	1	2	
Any*	-	107	30	0.82 (0.31,2.19)
	+	26	6	
Termination	-	47	19	0.67 (0.35,1.28)
	+	133	36	Adjusted 0.71 (0.26,1.38)
		Hydroxchloroquine		
		-	+	
Heart	-	126	24	1.75 (0.33,9.24)
	+	6	2	
Eye	-	129	26	-
	+	3	0	
Genitourinary	-	127	25	1.02 (0.11,9.14)
	+	5	1	
Hernia	-	131	26	-
	+	1	0	
Any*	-	107	22	0.78 (0.24,2.47)
	+	25	4	
Termination	-	46	13	0.70 (0.33,1.47)
	+	132	26	Adjusted 0.77 (0.36,1.61)
		Chloroquine		
		-	+	
Heart	-	127	90	0.94 (0.26,3.44)
	+	6	4	
Eye	-	130	92	0.94 (0.15,5.77)
	+	3	2	
Genitourinary	-	127	94	-
	+	6	0	
Hernia	-	132	91	4.35 (0.44,42.71)
	+	1	3	
Any*	-	107	83	0.54 (0.25,1.17)
	+	26	11	
Termination		47	34	0.98 (0.58,1.63)
		133	94	Adjusted 0.97 (0.57,1.67)

*Any malformations include heart, skull, eye, foot and genitourinary defects, central nervous system and hernias.
Adjusted for alcohol use, smoking, age (older or younger then 35) and folic acid use before and in the first trimester of pregnancy.

Discussion

This study did not identify any associations between the use of DMARDs and an increased risk of pregnancy terminations or birth defects. Second trimester use of azathioprine was associated with an increased risk of preterm birth.

Our results with respect to the risk of azathioprine use during the second trimester of pregnancy are similar to the results described by others. Nørgård et al (7) investigated the use of azathioprine throughout the entire pregnancy among women with Crohn's disease. They found a relative risk of 4.2 (1.4,12.5) for preterm birth associated with azathioprine use in group of women with Crohn's disease compared with women with Crohn's disease not using azathioprine. Goldstein et al (6) found an increased risk of preterm birth (OR 4.09 (2.0-80.6)) among a group of women receiving azathioprine for different indications including rheumatoid arthritis and inflammatory bowel disease. Their results suggest azathioprine use is associated with prematurity, although larger studies need to confirm these findings.

Hydroxychloroquine is often used in systemic lupus erythematosus (SLE), a rheumatic disease that has been associated with preterm birth (22). In this study two reference groups were used to investigate associations between preterm birth and DMARD use. If the use of a certain DMARD would be associated with preterm birth, it would be expected that an increase of the Odds ratio will be found in both comparison groups. After all, if the disease would be the underlying cause the OR would be close to 1 when compared with the group also having the disease while when compared to a group not having the disease would show an increased OR. In this study, the use of hydroxychloroquine in the second and third trimester of pregnancy and preterm birth showed an increased point estimate when compared with both reference groups although not significant. This would suggest that hydroxychloroquine might be a causal factor, however, hydroxychloroquine is mostly prescribed for SLE while it can be assumed that sulfasalazine is not very often prescribed for this disease. So whether the underlying disease is a confounding factor or that the drug use is associated with the increase can not concluded from this data.

We also included other birth defects when reviewing the birth defects among the women using a DMARD. However, since this is a very variable group of defects, they were not included in the final analysis. When investigating a relation between the increase of a certain birth defect and drug use, a detailed level of recording is necessary. It has been demonstrated that the completeness of recording of prescribing in the GPRD is high (19-21); however the recording of birth defects is not as detailed or complete. Meijer et al (23) showed that for the evaluation of birth defects, a detailed level of recording is necessary. In their study of EUROCAT data, they could not demonstrate any association between the use of clomiphene and hypospadias in general. However, when investigating the different forms of hypospadias, they found that the use of clomiphene was associated with the more severe form penoscrotal hypospadias. In our study, we investigated the associations between DMARD use and birth defects to generate hypothesis. If a significant association would be found this could be regarded as a signal and had to be tested in other databases such as EUROCAT central (24) or the Slone Epidemiology Birth Defect Study (25). We, however, did not see any significant association between birth defects in general and the use of DMARDs. It was noted that for the exposure to azathioprine, cyclosporin and chloroquine a rather high point estimated was seen in relation to a hernia, such an association might be worthwhile investigation further in the EUROCAT central database or Slone database. For most drug exposures and birth defects the numbers were to low to investigate the association at all and meaningful conclusion can therefore not be drawn.

In conclusion, this study our data showed that the use of azathioprine is associated with preterm birth. For a thorough evaluation of any association with birth defects, further data should be sought from the GPs contributing to the GPRD in order to obtain more detail regarding the birth defects identified. From the current data, no increase in the frequency of pregnancy terminations that come to the attention of the GP, and no major increase in risk of specific congenital malformations could be identified.

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Chapter 6

Treatment of pregnant and non-pregnant rheumatic patients. A survey among Dutch rheumatologists

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Abstract

Background

The aim of this study is to explore, among Dutch rheumatologists, aspects such as attitude towards guidelines, pharmacotherapy, and information needs in the treatment of pregnant as well as non-pregnant rheumatoid arthritis (RA) patients.

Methods

Fifteen rheumatologists from nine different hospitals were interviewed by means of a semi-structured interview. Questions addressing attitude towards guidelines, pharmacotherapy preferences and information needs with respect to the pregnant and non-pregnant patient were asked. The analysis will be based on descriptive statistics.

Results

Guidelines are used by almost half of the hospitals with respect to pregnant RA patients and by all hospitals for RA patients in general. With respect to pregnant women, nine respondents preferred stopping the medication as soon pregnancy is known. When treating RA patients, in general sulfasalazine and methotrexate would be drugs of first choice. Information is found in international and national books and guidelines.

Conclusion

Dutch rheumatologists are of the view that there is sufficient information on the treatment of RA in pregnant women or women wishing to become pregnant, except for safe use of medication during pregnancy. In the future, pregnancy risk categorization should be updated and discussed regularly. This should be based on more recent literature and experience. A good monitoring system for following all young patients with a rheumatic disease should be set up as a first step to collect more information on the safe use of medication during pregnancy.

Introduction

Use of medication during pregnancy is a delicate issue and physicians treating pregnant women always need to find a balance between the beneficial effects for the mother and the potential risks for the child. In Rheumatoid Arthritis (RA) induction of remission and its continuous maintenance is presently the goal of treatment[1]. Maintenance therapy with disease modifying anti-rheumatic drugs (DMARD) is considered necessary to achieve this objective[2,3]. Although fertility in RA is not impaired, pregnancy outcome is optimal when disease activity is limited both during conception and pregnancy. Continuation of drug use during pregnancy has been reported to be necessary for 10-25% of women with continuous active disease[4]. Fortunately, most women will experience an improvement of their RA symptoms during pregnancy, and medication can be tapered or even stopped during this period. However, medication use before pregnancy could still be necessary for disease control, and exposure to the drug in the early phase of pregnancy is therefore possible.

When treating young RA patients wishing to become pregnant, rheumatologists have to consider several issues. With active inflammation of the joints, when medication use is required to control the disease, the safety of pharmacotherapy is an important consideration. The treatment of RA has evolved rapidly in the past decade. In earlier (1994/1996) national and international guidelines[2,3,5] sulfasalazine (SSZ) was recommended as the initial DMARD for disease control when insufficient symptom control is obtained with non-steroid anti-inflammatory drugs (NSAID). By2002, the recommended initial DMARD therapy was methotrexate (MTX) or SSZ[1,6]. The shift from symptom control to disease control has implications for the treatment of young women wishing to become pregnant. MTX is thought to be a very effective DMARD as a general treatment of arthritis but it is a known teratogenic drug while SSZ is considered to be safe in pregnancy[7]. Little is known about how rheumatologists make their decisions in daily practice, concerning these issues. The aim of our study is to explore, among Dutch rheumatologists, aspects such as attitude towards guidelines, pharmacotherapy, and information needs and sources on the treatment of pregnant as well as non-pregnant rheumatic patients.

Methods

For this survey, we interviewed rheumatologists using in-depth semi-structured interviews. All rheumatologists and rheumatologists in training in the Northern and Eastern part of the Netherlands were informed about this survey (n=42). They worked in nine different hospitals; one academic hospital (1307 beds), 6 teaching hospitals (between 381-1127 beds) and 2 regional hospitals (340 and 985 beds) (table 1).

Table 1. Characteristics of the respondents and the hospitals (N=15)

Characteristic	Number
Location of hospitals	
- North	4
- East	5
Type of hospitals	9
- Academic hospital	1
- Teaching hospital	6
- Regional hospital	2
Number of beds per hospital	
- < 500	2
- 500-1000	4
- >1000	3
Respondents	15
- Rheumatologist	14
- Rheumatologist in training	1

In the interview, several issues were addressed by means of open-ended questions. We asked questions about RA treatment in pregnancy, whether they could give an indication of how many pregnant patients with RA attended their practice per year and the kind of information they give these patients.
We also asked about their attitude towards guidelines or protocols, whether they used guidelines when treating pregnant RA patients, and if so, which guidelines they used, what reasons they had for deviating from the guidelines and whether

they had any agreement with colleagues in other disciplines about the treatment of their pregnant RA patients. We asked the respondents for their preferences in the pharmacotherapy of a pregnant RA patient, and the reasons for their choices and when they would deviate from their regular choices. We ended our interview by asking if there were enough sources of information, from their point of view, for the optimal treatment of pregnant women with RA.
Because we were also interested in the treatment of RA patients in general, we included questions relating to general treatment. All participants were interviewed in a face-to-face semi-structured interview carried out by one of the researchers (FV). The interviews took place from June till October 2005 in the office of the rheumatologist. All interviews were taped and notes were made as well. Afterwards the interviews and notes were transcribed into the exact wording of the participants and these were summarized into short conclusions or statements, stratified by topic or question.

Results

All hospitals appointed one, two or three rheumatologist to be their spokesman. From every hospital at least one rheumatologist was involved, in total 16 rheumatologists were appointed. Fifteen rheumatologists agreed to participate, nine men and six women, among them one rheumatologist in training (table 1).

Treatment of pregnant patients or patients with a pregnancy wish

Each of the 15 respondents reported seeing at most 20 pregnant patients per year, mainly RA patients. From the nine hospitals in this survey, five indicated not using specific written guidelines for the treatment of pregnant RA patients or those wishing to become pregnant. Four hospitals reported using written guidelines; two hospitals included a section ‘pregnancy’ in their information leaflet and two other hospitals used guidelines which contained relevant information such as pregnancy risk classifications, and background information about known or possible teratogenic effects.
From Table 2 can be seen that, nine rheumatologists (9/15) recommended their patients to stop medication as soon as pregnancy was known.

Table 2. Preference of respondents (n=15) in pharmacotherapy of pregnant rheumatoid arthritis and rheumatoid arthritis patients in general

	MTX*	SSZ	LEF	HCQ	AZA	Corticosteroids	No drugs
Pregnant							
1st choice	0	4	0	0	0	2	9
2nd choice#	0	5	0	0	3	3	-
3rd choice#	0	1	0	2	0	3	-
In general							
1st choice	13	2	0	0	0	-	-
2nd choice	1	10	1	3	0	-	-
3rd choice#	1	2	5	5	0	-	-

* MTX=methotrexate, SSZ=sulfasalazine, LEF=leflunomide, HCQ=Hydroxychloroquine, AZA=Azathioprine, # some respondents reported only one or two drugs of choice.

The existence of guidelines, or the type of hospital, did not influence this. All rheumatologists indicated that for SSZ, MTX and Leflunomide (LEF), what to do when a woman wanted to become pregnant, was clear. For Azathioprine (AZA), Cyclosporine (CSP) and Hydroxychloroquine (HCQ), this was less so. Some rheumatologists (5/15) indicated that AZA, CSP and HCQ could be used if necessary although careful considerations were needed. However, most rheumatologists (10/15) disposed towards not giving these medications to pregnant women. Based on the available information, rheumatologists advised stopping MTX and LEF for at least three months before pregnancy was intended. In theory SSZ could be continued during pregnancy because it is thought to be safe. They obtained their information from international and national books[8,9], international literature (by pub-med and up-to-date), international and national guidelines[1,6,10], and from colleagues.

Generally, patients with RA were referred to a gynecologist when necessary only, such as with the presence of severe RA, or the use of some DMARDs (AZA) or steroids and at the patient's request. Only two rheumatologists indicated that they referred all their RA patients to a gynecologist. For patients with a systemic

disease, such as Systemic Lupus Erythematosus (SLE), referral to a gynecologist was more usual, because of the expected complications[11].
Most rheumatologists (11/15) thought that there was sufficient information/guidelines on the treatment of a pregnant woman, although some (5/15) would like to see national guidelines. The lack of evidence was considered to be the largest problem.

Treatment of rheumatic patients in general
Table 2 shows that, MTX is the drug of first choice in the treatment of RA patients for 87% (13/15) of the rheumatologists interviewed; for 13 % (2/15), SSZ was preferred as the first choice DMARD. HCQ, LEF and anti-Tumor Necrosis Factor (anti-TNF) therapy were often considered after failure of the first and, sometimes, second choice. Combinations of the different drugs were tried if necessary.
Three hospitals used guidelines to formulate their own protocols and implemented them. These general guidelines, including points of view, based in the international literature[10] were formulated by the Dutch Society of Rheumatology. The guidelines were designed to be implemented after adaptation for regional or local settings. In the Northern region, four hospitals developed a joint protocol based on those recommendations, and in the east two hospitals did the same for their region. Thirteen of the fifteen rheumatologists interviewed, indicated using the guidelines as written; two rheumatologists said they followed some protocol but did not used these written ones. Reasons for rheumatologists not following the guidelines were patient-related.
All rheumatologists reported having some agreements with the GP. In 2002 a committee of rheumatologists and general practitioners (GP) formulated a set of guidelines regarding the tasks of rheumatologists and GP's in the treatment of patients with RA[12]. Proposals were made with the advice that for implementation, guidelines ought to be adjusted to take account of local and regional settings. Some hospitals (3/9) implemented the proposals made; others reported not using them at all (4/9) or suggested non-feasibility (1/9) in their practice or satisfactory existing agreements between the GP and the rheumatologist (1/9).

Discussion

Our survey showed that although rheumatologists acknowledged that the evidence regarding use of RA medication during pregnancy was scarce, there was no major need for supplementary guidelines.

The lack of evidence is rather obvious. Women who might become pregnant are excluded from human trials conducted before drug approval[13]. Moreover, formal trials on use of registered drugs during pregnancy are hindered due to ethical considerations. Information about approved drugs during pregnancy is usually based on, generally scarce, off-label use.

The rheumatologists interviewed in this study reported seeing at most 20 pregnant patients each per year. This indicates that the group of women using DMARDs during pregnancy is very small, and experience of such use will remain limited. If a patient is pregnant or wishing to become pregnant, a tailor-made advice, based on the characteristics of the individual patient, is given. Therefore most rheumatologists felt that general guidelines probably would not contribute to better advice.

All rheumatologists interviewed indicated that guidelines, and literature on use of SSZ, MTX, and, LEF during pregnancy were clear. They advised stopping MTX and LEF at least three months before intended pregnancy, in accordance with national and international guidelines[1,3,10]. Some rheumatologists indicated that AZA, CSP and HCQ could be used, after careful consideration, if necessary. Our recent review [14] suggests that for HCQ, the information from the US FDA pregnancy risk categorization[8] is somewhat in conflict with recent evidence. HCQ is categorized as C according to the US FDA pregnancy risk category, stating that safety in human pregnancy has not been determined. The evidence we reviewed suggests that HCQ is probably safe when used in moderate dosages during pregnancy for treatment of SLE or RA. AZA is categorized as a drug that despite indications of fetal risks can be considered during pregnancy if the benefits of therapy outweigh the potential risks. Our review suggests that AZA seems to be generally safe in pregnancy. Nevertheless is AZA categorized as a D drug, and most clinicians will therefore choose not to use it drug during pregnancy.

Chakravarty et al.[15] described the practices of rheumatologists in the US when prescribing several DMARDs such as MTX, LEF and some anti-TNF-α drugs to women of childbearing age. Respondents agreed strongly that MTX and LEF were contraindicated in pregnancy and that reliable methods of birth control should be used. Those results are in agreement with the recommendations given by our respondents, to stop MTX and LEF at least 3 months before intended pregnancy. We did not explicitly asked about advice on contraceptives methods, when taking these drugs. With regard to all other medications, most rheumatologists advised women to stop as soon as they knew they were pregnant, or at least within two weeks of the start of pregnancy. This raises the question of whether drug use this early could influence pregnancy outcome.

MTX and SSZ were found to be the DMARD of first choice, in agreement with several studies from different countries (Table 3). An Australian survey by Conaghan et al.[16] reported that the drug of first choice for young people was SSZ, but did not present the reasons for this. Jobanputra et al.[17] found that, aside form MTX and SSZ being the drugs of first and second choice, LEF was more commonly preferred than intramuscular gold as third choice. In our study LEF was also mentioned as a third choice by several rheumatologists. Gold was mentioned as such by only two rheumatologists, one of whom had ceased using it.

Table 3. DMARD preferences in the treatment of Rheumatoid Arthritis in gneral from surveys according to rheumatologists in different countries

Author (Reference)	Year of publication	Country	DMARD preference
Kay et al.[20] Abstract	1992	United Kingdom	Sulfasalazine was the most popular first choice DMARD
Conaghan et al.[16]	1997	Australia	MTX was the most frequently used DMARD, drug of first choice for young people was SSZ
Maetzel et al.[21]	1998	Canada and United States	MTX first choice for 78.5% of the US respondents and 68.7% of the Canadian rheumatologists
Caballero-Uribe et al.[22]	1999	Colombia	Rheumatologists favor MTX, CQ, and HCQ
Zink et al.[23]	2001	Germany	Median prescription rate in 1998 for MTX was 55%, for SSZ 15% and for antimalarials 8%
Pope et al.[24]	2002	Canada	MTX and HCQ prescribed by all rheumatologists and SSZ by 98%, but did not look at order of preference
Aletaha et al.[25]	2004	Interna-tional	MTX first choice, followed by SSZ
Maravic et al.[26]	2004	France	MTX recommended in early RA treatment by 46% and SSZ by 8.2%
Jobanputra et al.[17]	2004	United Kingdom	MTX and SSZ were preferred and LEF was more commonly preferred then intramuscular gold

DMARD=Disease Modifying Anti Rheumatic Drugs, MTX=Methotrexate, SSZ=Sulfasalazine, CQ=Chloroquine, HCQ=Hydroxychloroquine, LEF=Leflunomide

The changes in the pharmacotherapy of RA treatment, over recent years are reflected in the different guidelines. Pollemans et al.[18] reported in 1996 that Dutch rheumatologists and GPs recognized that cooperation between them needed improvement. Guidelines for such cooperation were published in 2002 by a committee of rheumatologists and GPs[12]. Our study shows that all rheumatologists reported having agreements with GPs, although not used those guidelines.
Using a semi-structured interview as a technique for collecting data is a strength of this study. Most surveys of rheumatologists have used questionnaires, sent to large groups of rheumatologists. With this kind of survey low response rate is a problem. A semi-structured interview results in higher response rates[19].
Only including rheumatologists from northern and eastern Netherlands might be considered a weakness of this study. Therefore, the generalizability of the results to the whole Netherlands is tenuous.
Dutch rheumatologists regard the available information as being sufficient to guide treatment of RA in women who are pregnant or wishing to become pregnant, despite inadequate evidence on safe use of medication during pregnancy. There are several options to reduce this problem. First, pregnancy risk categorizations, such as the US FDA risk categorization, need to be regularly updated. Secondly, we plead for a good monitoring system, to follow all young patients with a rheumatic disease, to enable collection of information on safe medication use during pregnancy. Greater insights on the perspective of pregnant women or those intending to be are also required.

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Chapter 7

Drug use during pregnancy; asking questions and finding answers for women with a rheumatic disease

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Submitted

Abstract

Purpose

Evidence of drug use and pregnancy is scarce and often inconsistent. This study aims to explore questions women with rheumatic diseases have and answers they retrieve on drug use and pregnancy.

Method

Trough the Rheumatism Patient Federation website, women with rheumatic diseases who desire to become pregnant (now or in the past), who are pregnant, or recently gave birth could request a questionnaire. Information about patient demographics, current and intended drug use, and questions on drug use and pregnancy were asked.

Results

Of the fifty women returning the questionnaires, 66.0% judged their questions to be answered satisfactory, 42.0% found information available to them sufficient. 61.2% reported that doubts and/or fears did not change or increase after receiving the information.

Discussion

Most women find their questions on drug use and pregnancy answered but information available to them is insufficient. Doubts and/or fears remained or increased after receiving the information.

Introduction

In many chronic conditions pharmacotherapy is required as part of disease treatment, however, when pregnancy is considered, questions about (dis)continuation of drugs arise.

Lack of evidence on drug use during pregnancy in rheumatic diseases affects patients as well as rheumatologists. For some drugs recommendations are clear[1]: methotrexate, presently the anchor drug in rheumatic diseases, can not be used during pregnancy due to its teratogenic effects[2-4]. Sulfasalazine can be used safely, although teratogenic risk can never be excluded[2]. For other drugs, information is considered to be less clear[1]; for the use of azathioprine and hydroxychloroquine benefits of continuation may outweigh potential risks for the fetus[2-5]. For other drugs such as Tumor Necrosis Factor alfa (TNFα) and leflunomide information on use in pregnancy is scarce[2,4,6,7].

Women with rheumatic diseases who desire to become pregnant may not only have questions about the disease and how to care for the child once it is born, but also may have questions about pharmacotherapy before, during or after pregnancy. In seeking answers to their questions, women might consult their rheumatologist, general practitioner (GP) or community pharmacist[8]. Answers to their questions might influence the woman's decision to become pregnant or choices on drug use before, during or after pregnancy. In order to provide the care needed by these women, health care-providers must know about the need for information on drug use and pregnancy. To our knowledge no studies have been performed to investigate these needs and questions. Therefore, this study aims, from the perspective of women with a rheumatic disease to survey: whether women have questions about drug use and pregnancy; whom they ask these questions; and whether their questions are answered.

Methods

Trough an announcement on the Rheumatism Patient Federation (Reuma Patienten Bond) website women were invited to participate in our study. Respondents were asked to fill out a questionnaire which was sent to them by mail with an explanation letter and free return envelope.

The questionnaire consisted of three sections. The first section contained questions about the woman's demographic features, including age and diagnosis. In addition women had to indicate if she was pregnant, recently gave birth, if she desired to become pregnant or if she had had the desire to become pregnant in the past but no longer at the time of the questionnaire.

The second section focused on drug use before, during pregnancy and after pregnancy, if appropriate. Every woman was asked to report on drug use in the periods before pregnancy: one period in which the woman did not yet have the desire to become pregnant and a second period in which she consciously wanted to become pregnant. Drug use had to be reported separately for both periods. Via a multiple-choice question, the woman was asked to indicate reasons for choosing these drugs; answers included own initiative, initiative of the rheumatologist or GP. Women, who were not pregnant (yet) at time of the questionnaire, were asked their intention of taking drugs during and after pregnancy and why they would choose to do so. Women who were pregnant had to indicate their drug use during pregnancy, and if and why they intended to use drugs after pregnancy. Women, who recently delivered a baby, were asked to report their drug use during and after pregnancy and their reasons for this. Women, who had the desire to become pregnant in the past but no longer at time of the questionnaire, were asked to indicate why they gave up this desire and if this involves doubts or fears about their drugs or disease. They were asked to indicate where these doubts or fears originated.

In the third section of the questionnaire patients were asked if they had any questions about drug use and pregnancy. The questions were divided into five pre-defined multiple-choice topics: drug use before and during pregnancy, drug use during breastfeeding, disease relapse after pregnancy, and harmfulness of the drug to their baby. Questions not directly related to these predefined topics were reported as other.

By means of pre-defined answers women were asked to indicate where or to whom they asked their questions (e.g. rheumatologist, GP, pharmacist, Internet, or other). If a question was not answered to a woman's satisfaction, she had to indicate if she posed her question(s) somewhere else.
The National Association of Rheumatic Patients (Reuma Patienten Bond) and Dutch league against Rheumatism have a leaflet on rheumatic diseases, genetics and pregnancy and their website contains information on pregnancy. Women were asked to indicate whether they have read this information and if they were satisfied with the information given. The section ended with five propositions which could be answered on a 6-point-Lickert scale (strongly disagree to strongly agree). Respondents were asked to indicate to what extent they agree or disagree on the following topics: sufficiency and clarity of the information available to them, appreciation of a specific leaflet on pregnancy and drugs, reassurance due to the information on drug use during pregnancy. Finally, patients were asked to indicate if the information available to them decreased, did not change, or increased any doubts and/or fears about drug use during pregnancy. The authors based the analysis on descriptive statistics.

Results

During a period of three months (February 1st to May 1st, 2007) 55 women requested a questionnaire, 50 questionnaires (90.9%) were returned (table 1, Demographics). Thirty-one women (62.0%) desired to become pregnant, eight women (16.0%) were pregnant, seven women (14.0%) had recently given birth, and four women (8.0%) expressed a past desire to become pregnant.

Table 1. Demographic results, including average age at time of the questionnaire and at time of diagnosis and the reported diagnosis of all women (N=50)

Age at time of questionnaire (mean, ±SD)	33.2 (±4,1)
Age at time of diagnoses (mean, ±SD)	24.7 (±6.0)
Diagnoses	
Rheumatoid Arthritis	33 (66%)
Ankylosing spondylitis (Bechterew's disease)	11 (22%)
Psoriatic arthritis	2 (4%)
Fibromyalgia	2 (4%)
Systemic Lupus Erythematosus	1 (2%)
Sjögren's syndrome	1 (2%)
Polyarthritis	1 (2%)
Mixed Connective Tissue Disease	1 (2%)
Arthritis	1 (2%)

Reported drug use

Reported drug use showed that the use of methotrexate and TNFα drugs decreased as soon women consciously want to become pregnant, reported use of sulfasalazine increased during this period. Besides DMARDs women reported using NSAIDs, corticosteroids, or no drugs. The choice for a certain drug regime is mainly based on advice of the rheumatologist or on the woman's own initiative after consulting her rheumatologist. Of the women who reported using sulfasalazine (n=17) or other DMARDs (gold or azathioprine (n=5)) at any time before their (potential) pregnancy, around 80% reported receiving a satisfactory answer to their question(s) (table 2).

Table 2. Percentage of women receiving a satisfied answer to the questions asked and percentage of women who reported a decrease, increase or no change in doubts after reading or receiving information on the use of their drugs during pregnancy among women who reported a certain drug use before their (potential) pregnancy.

Reported drug use before (potential) pregnancy (N=50)		Satisfied answers to questions	Doubts, after reading/receiving all available information, about their drug use during pregnancy*		
			%		
	N	%	<	=	>
Methotrexate	27	66.7	29.6	55.6	14.8
Sulfasalazine	17	82.4	41.2	35.3	35.3
Hydroxychloroquine	10	40.0	30.0	40.0	20.0
TNF-α	14	37.1	35.7	42.9	21.4
Other DMARDs[1]	5	80.0	40.0	60.0	0.0
NSAID	38	63.2	44.7	42.1	10.5
Corticosteroids	22	59.1	31.8	50.0	18.2
Miscellaneous	18	61.1	38.9	44.4	11.1
No drugs	7	57.1	57.1	28.6	14.3

*<decreased, =did not change, >increased1 Other DMARDs including: ciclosporin, aurothiomalaat, azathioprine, and leflunomide

Of the women who reported using TNFα-drugs (n=14) or hydroxychloroquine (n=10), respectively 37.1% and 40.0% reported being satisfied about the answers. Of the women who reported not using drugs (n=7) before pregnancy, 57.1% indicated a decrease in their doubts and/or fears. For women using methotrexate (n=27), corticosteroids (n=22), or other DMARDs (n=5), respectively 55.6%, 50.0% and 60.0% reported no change in doubts and/or fears about their drug use. Of the women who reported to use sulfasalazine (n=17), 35.3% indicated an increase of doubts and/or fears. Four women gave up their desire to become pregnant, mainly due to fears and doubts about their medication and disease as a result of a lack of information available to them.

Information

The information leaflet from the Dutch Association of Rheumatic Patients was read by 30 women (60.0%), of whom 17 (56.7%) were satisfied with the information in this leaflet. Seventeen women (34.0%) read the information available on the website of the Dutch League Against Rheumatism, 41.2% (n=7) of these women were satisfied with this information.

In general, the information on drugs and pregnancy available to them was found to be sufficient for 42.0% (n=21) of the women, 48.0% (n=24) found the information clear. For 62.1% (n=30) of the women, possible doubts and/or fears increased or did not change due to information available to them. For 86.0% of the respondents (n=43) a specific leaflet on pregnancy and drugs would have added value.

Questions

All women reported having questions, mainly about drug use before and during pregnancy and about potential harm of the drug to their baby. There is no difference between the questions from women with a current or past desire to become pregnant and those who are pregnant or recently gave birth (table 3).

Table 3. Number of women (percentage) who reported to have asked questions about these topics in a group of women with a current or past desire to become pregnant and in a group of women who are pregnant or recently gave birth at time of the questionnaire.

Question	Women with a current or past desire to become pregnant (n=35)	Women who are pregnant or recently gave birth (n=15)
Medication before pregnancy (N (%))	34 (97.1)	14 (93.3)
Medication during pregnancy (N (%))	35 (100)	14 (93.3)
Harmfulness for my baby (N (%))	32 (91.4)	14 (93.3)
Relapse of disease after pregnancy (N (%))	26 (74.3)	12 (80.0)
Medication and breastfeeding (N (%))	26 (74.3)	13 (86.7)
Other questions (N (%))	10 (28.6)	2 (13.3)

Two-thirds of all women (n=33) received satisfactory answers to their questions, 32.0% (n=16) did not. The latter were mainly women who wanted to become pregnant at time of the questionnaire. Fourteen out of the 16 women reported re-asking their question(s), three women received a sufficient answer(s) the second time. Table 4 shows that questions were posed to professionals, mainly the rheumatologist. Women with a current or past desire to become pregnant also used the media (48.6%), friends and family (17.1%), and others (14.2%) as a source of information. Women who were currently pregnant or recently had given birth reported using the media (33.3%) as another source of information.

Table 4. Number of women (percentage) who reported to have asked questions to a certain medium e.g. professionals, media, etc in a group of women with a current or past desire to become pregnant and in a group of women who are pregnant or recently gave birth at time of the questionnaire.

Medium		Women with a current or past desire to become pregnant (n=35)	Women who are pregnant or recently gave birth (n=15)
Professionals	N (%)	35 (100)	15 (100)
Rheumatologist	N	35	15
Gynaecologists/midwives	N	13	7
Rheumatology nurse	N	11	2
General practitioner	N	10	3
Pharmacist	N	5	2
Media*	N (%)	17 (48.6)	5 (33.3)
Direct environment*	N (%)	6 (17.1)	-
Others	N (%)	5 (14.2)	-
Not asked	N (%)	10 (28.6)	2 (13.3)

*Media includes Internet, Rheumatism call centre, Rheumatism patient Federation; direct environment include family and friends

Discussion

Our survey of women with rheumatic diseases and a (recent) pregnancy or (past) desire to become pregnant showed that these women have many questions about

drug use and pregnancy. The questions were mostly answered to their satisfaction. However, the majority of the women found the information available to them insufficient and reported that doubts and/or fears about drug use and pregnancy increased or did not change due to the information.

It is generally believed that uncertainty and insufficient information may increase fear[9].

A recent study[1] among rheumatologists showed that recommendations towards drugs such as azathioprine and hydroxychloroquine were found less clear, this might lead to uncertainty for rheumatologists and patients. It is possible that the information available to them was insufficient for the women and led to questions. These questions were then posed to and answered by, for example the rheumatologists. This might explain why 66.0% reported to be satisfied with the answers they received. To what extent this is true for participants in our study could however not be determined. Leeners et al.[9] reported 31.4% satisfaction with medical information received by a group of women with hypertensive disorder in pregnancy. Although these groups can not be compared, it is clear from both studies that available information is often insufficient.

Katz[10] reported that concerns about medication issues and being able to care for a child most commonly affected childbearing decisions in women with a rheumatic disease. Women in our study reported that fears and/or doubts about their medication and disease were indeed the main reasons for giving up the desire to become pregnant.

Reported use of sulfasalazine increased when women consciously want to become pregnant. Sulfasalazine is thought to be safe during pregnancy which was found to be well-defined by rheumatologists[1,2]. This might explain why the majority of the women using sulfasalazine before pregnancy reported their questions to be satisfactorily answered. However, a relative large proportion (35.3%) indicated that doubts and/or fears about their drugs and pregnancy increased. Reluctance towards using drugs during pregnancy may exist, and safe use of sulfasalazine during pregnancy might be hard to believe for these women.

Reported methotrexate and TNFα-drug use decreased as soon as women consciously wanted to be become pregnant. Guidelines recommend to stop

methotrexate least one ovulatory cycle before trying to conceive[1-4]. When using a TNFα-drug effective measures towards contraception should be taken[2]. Women using TNFα-drugs before their pregnancy were less satisfied with the answers. This might be explained by a lack of evidence on use of TNFα-drugs during pregnancy. Recommendations for hydroxychloroquine use during pregnancy were less clear[1], which might explain why only 40.0% of the women using hydroxychloroquine before pregnancy reported receiving a satisfactory answer. Six women reported not using any drugs at time she consciously wanted to become pregnant. The results from this study are consistent with the study among rheumatologists; they indicated a preference to stop medication if possible, or, if a drug had to be used, they preferred sulfasalazine[1].

Our study suggests that the rheumatologist, as the primary health care provider, is the major source of information[9]. And, although not suggested by the results of this study, physicians and GP's are also often consulted about drug use during pregnancy[11]. The Internet, an almost unlimited information source[9], was used by a small proportion of the participants in our study, which was also seen by Norum et al.[12].

Questionnaires can have a low response rate, though the response to our questionnaire was high (90.9%). The high response rate was possibly due to the way women were invited to participate. Women had to send in a request for the questionnaire, therefore indicating a willingness to fill out the questionnaire. The number of women who in principle were eligible for inclusion in our study and yet did not request a questionnaire is unknown. The results from this study are not representative of the general population since the questionnaire was specifically designed and set up for patients with a rheumatic disease.

In conclusion, women with a rheumatic disease who want to become pregnant have a lot of questions about drug use before, during, and after pregnancy. Fortunately, most of these women get their questions appropriately answered. Available information on drug use during pregnancy is insufficient and doubts and/or fears on drug use and pregnancy remain or have increased. Rheumatologists should regularly be updated about drugs they prescribe to women of childbearing age in order to respond to their patient questions and needs with

most current knowledge. To gather more knowledge on drug use during pregnancy in women with a rheumatic disease, setting up a monitoring system following these women from start of diagnosis throughout pregnancy should be considered.

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Summary and General Discussion

Summary

Rheumatic diseases occur in about two third of the Dutch population, about 10% of them is of childbearing age. An early and effective treatment is of great necessity and the development of new drugs are necessary. The last decades many new drugs were developed in the treatment of rheumatic diseases, such as several TNFα drugs (Tumor Necrosis factor). Drugs such as methotrexate and azathioprine, used as an anti-cancer drug and immunosuppressive drug after transplantation respectively, were also introduced in the treatment of rheumatic diseases. All these drugs are considered to be part of the disease modifying anti-rheumatic drugs (DMARDs).

The get some inside on the current knowledge on the safety of these DMARDs during pregnancy, chapter 1 reviews the studies describing the safety of DMARDs during pregnancy. The review underscores the gross absence of data on safety and risks of DMARDs before and during pregnancy. Follow-up studies and case-control surveillance are suitable to identify teratogens after marketing approval. Apart from two case-control studies and one cohort, mostly small exposed cohorts or individual cases were studied, as could be seen in the review. Methotrexate is categorized as X by the FDA, meaning that the possible risk clearly outweighs any positive benefits. The results presented in the review reconfirm this status. Azathioprine is categorized as a drug that despite indications of fetal risks can be considered during pregnancy if the benefits of therapy outweigh the potential risks. The results shown in the review are in line with these recommendations, azathioprine seems to be generally safe in pregnancy. Sulfasalazine is also considered to be generally safe during pregnancy, which was underscored by the studies described in the review. Results of the studies presented in the review with respect to hydroxychloroquine suggest that this drug can be safely used during pregnancy in the treatment of SLE (systemic lupus erythematosus) and RA (rheumatoid arthritis) in moderate dosages, which is in contrast with the FDA categorization. However, it must noted that these conclusions are based on small exposed cohorts. With respect to the other DMARDs, such as leflunomide, gold preparations and TNFα drugs, information is even more limited; only small exposed

cohorts or case reports were found. Because pregnant women are usually excluded from clinical trials, case-reports and case-series are the first signals for the clinical practice of an adverse effect or pregnancy outcome after drug use. However with respect to DMARDs these case reports and case-series were almost never followed by analytical studies as case control surveillance or follow up studies. Perhaps more time is needed to collect enough data to conduct proper case-control or cohort studies.

Chapter 2, 3 and 4 were performed to see whether DMARDs and another group of anti-rheumatic drugs, NSAIDs (non-steroidal anti-inflammatory drugs), were used before and during pregnancy. If these drugs would not have been used during pregnancy, safety would not have been an issue. However, as is shown in these chapters, DMARDs as well as NSAIDs were used before and during pregnancy. With respect to NSAIDs (chapter 2), a warning was issued in 2005 by the EMEA (European Medicines Agency) about the use of these drugs in the first two trimesters of pregnancy. Based on recent studies, which describe associations between NSAIDs and several different birth defects, it was recommended not to use these drugs in the first trimesters unless strictly indicated. In a drug utilization study based on IADB.nl prescription data, we showed that in 3.9% of the pregnancies NSAIDs (or Acetylsalicylic acid) were prescribed during pregnancy, in 2,9% of the pregnancies these drugs were prescribed during the first trimester. Data on over-the-counter use of NSAIDs was not included in this study, so it is assumed that the actual NSAID use is even higher. Our data show the prescribing of NSAIDs before the warning issued by the EMEA, it is therefore necessary to further investigate the prescribing of these drugs after the warning issued in 2005.

Chapter 3 describes the use of sulfasalazine, azathioprine and methotrexate round pregnancy. Results showed that 35 women received a prescription for sulfasalazine, azathioprine and/or methotrexate before their first pregnancy. Methotrexate was not continued during pregnancy, which is in accordance with national and international guidelines. Azathioprine was continued during pregnancy by 60% of the women who received this drug also before pregnancy, for sulfasalazine 38% of the women continued their drug during pregnancy. Co-medications of women receiving sulfasalazine as their initial DMARD are anti-

inflammatory and anti-rheumatic drugs and analgesics. For women receiving azathioprine as their initial DMARD corticosteroids and intestinal anti-inflammatory drugs were mostly prescribed as co-medication. No specific prescription patterns were found in the use of DMARDs among pregnant women. Based on the results presented in chapter 3 it was concluded that prescribing of DMARDs and related co-medication is based on the characteristics of the individual patient.

In chapter 4 the General Practice Research Database (GPRD), was used to investigate the prescribing of DMARDs before and during pregnancy in the UK general practice.

The results showed that in 1100 pregnancies a DMARD was prescribed just before or during pregnancy. Most often the drugs were prescribed as a malaria prophylaxis (chloroquine), but also azathioprine, hydroxyhloroquine and sulfasalazine were prescribed. Methotrexate and leflunomide were prescribed less often. The majority of the women to whom sulfasalazine or azathioprine was prescribed in the three months leading up to pregnancy, continued to have them prescribed during pregnancy. The other drugs were mainly stopped during the first trimester of pregnancy. Methotrexate was continued during pregnancy in some cases, this is not in accordance with national prescribing guidelines. Reasons for continuation of this drug can not be obtained using this database, but might partly be explained by unplanned pregnancies. In general, the prescribing of DMARDs around pregnancy decreased; this may be partly owing to guidelines being followed but also owing to the uncertainty of DMARD safety during pregnancy. For most products the frequency and duration of exposure increased in the second trimester of pregnancy compared to the previous period. The differences found between the use of DMARDs during pregnancy in the Netherlands and the UK might be explained by cultural differences or by the use of a different kind of data. The detailed information on DMARD exposure and available information about diagnoses and birth outcome in the GPRD can be used to evaluate any associations between DMARD exposure and selected birth outcomes, which has been described in chapter 5. No increased risk of pregnancy termination or general congenital malformations associated with any DMARD during the first trimester was noted. The use of azathioprine in the second trimester was associated with an

increased risk of preterm birth when compared with women to whom no DMARD was prescribed at all (OR 3.25 95%CI 1.82-5.78). Similar results associating azathioprine use with preterm birth were found in other studies, although larger studies are needed to confirm the findings. The results also showed an increased relative risk (odds ratio), although not significant, of preterm birth related to 2nd and 3rd trimester exposure of hydroxychloroquine. Hydroxychloroquine is mostly prescribed in SLE and SLE has been associated in earlier studies with preterm birth. Whether the underlying disease (SLE) is the confounding factor or that the drug is associated with this increase, could not be concluded from our data. This study was conducted to investigate the associations between DMARD use and birth defects to generate hypothesis. When investigating a relation between the increase of a specific birth defect and drug use, a detailed level of recording is necessary. It has been demonstrated that the completeness of recording of prescribing in the GPRD is high; however the recording of birth defects is not as detailed and complete. It was noted that for the exposure to azathioprine, cyclosporin and chloroquine a rather high relative risk (point estimated) was seen in relation to a hernia although not significant.

Besides insight on the use and safety of DMARDs during pregnancy, insight on current clinical practice is of importance to see whether for example treatment or counseling needs to be changed. Interviews with rheumatologists (chapter 6) revealed that although the evidence with respect to the use of DMARDs during pregnancy is scarce, there was no major need for supplementary guidelines. The lack of evidence was rather obvious and also shown in the review (chapter 1). Guidelines with respect to the use of sulfasalazine, methotrexate and leflunomide during pregnancy were clear, according to the respondents. Sulfasalazine can be continued during pregnancy, the latter two need to be stopped before conception. The respondents also indicated that drugs such as azathioprine, cyclosporine and hydroxychloroquine could be used during pregnancy if necessary and after careful consideration. Methotrexate and sulfasalazine would be the drug of first choice in regular treatment of RA. However, in pregnancy the rheumatologist indicated a preference for sulfasalazine or discontinuation of the drugs at all. Experience with pregnancy was mostly limited, at most 20 pregnant patients or patients wishing to

be become pregnant were annually seen by the rheumatologists. Therefore rheumatologists give their patient a tailor made advice, based on the individual characteristics. It was felt that guidelines would probably not contribute to a better advice. Overall, the Dutch rheumatologists are of the view that there is sufficient information on the treatment of RA in pregnant women or women wishing to become pregnant.

In the last chapter we describe women's experience; what are their questions when using DMARDs and having a child wish. By means of a questionnaire women with a rheumatic disease were approached (n=50) to explore the questions they had and answers they retrieved about drug use and pregnancy. Most women were diagnosed with rheumatoid arthritis or Ankylosing spondylitis. The reported use of methotrexate and TNFα drugs decreased as soon as women consciously want to become pregnant, the reported use of sulfasalazine increased. About two-third of the women responding to the questionnaire indicated that their questions were satisfactory answered. Most reported questions were about medication use before and during pregnancy and the harmfulness for the baby. Women indicated that the rheumatologists and the media (including internet) were the most reported sources for information and answers to their questions. About forty percent judged that the available information is sufficient, the majority of the women indicated that a specific leaflet on pregnancy and drugs would be of added value. Doubts and/or fears remained or increased after receiving information for the majority of the women.

This thesis explored the field of DMARD and drug use during pregnancy. From literature it was shown that there is a gross absence on safety data of DMARD use during pregnancy. This was indicated by rheumatologists and patients as well. In line with these findings, the patients expressed a need for a specific leaflet on pregnancy and drug use. Rheumatologists, however, indicated that there was no major need for supplementary guidelines. DMARDs are being used before and during pregnancy, however a specific pattern was not found. From the data it can be concluded that the patients receive a tailor made advice with respect to drug treatment during pregnancy, which was also indicated by the rheumatologists.

From the safety data it became clear that DMARDs were not associated with any specific birth defects. An increased association between azathioprine use in the second trimester and pre-term birth was seen but these finding should be confirmed by larger studies.

General discussion

This thesis aimed to explore in particular a safer use of disease modifying anti-rheumatic drugs (DMARDs) among female pregnant patients. On the one hand, post marketing studies can be performed not only to identify the use of DMARDs but also to see whether these drugs are prescribed according to guidelines. Subsequently, the safety of these drugs during pregnancy can be determined by performing risk assessment studies (follow-up or surveillance). On the other hand, it has to be identified whether women using DMARDs or rheumatologists prescribing DMARDs encounter difficulties regarding the use/prescribing of these drugs during pregnancy.

The complexity of elements involved

A young patient with a rheumatic disease wishing to become pregnant, is not a situation a rheumatologists encounters on a daily basis (chapter 6). The woman will have questions specifically about her disease and the use of her drugs in relation to pregnancy (chapter 7). According to rheumatologists recommendations on drugs such as sulfasalazine and methotrexate before and during pregnancy are clear. However, for more recent introduced drugs such as TNFα-drugs recommendations are less clear, mainly due to the lack of evidence on these drugs (chapter 1 and 6).

The example shown in box 1 shows that not only women using DMARDs have questions, also rheumatologists have questions about the drugs they prescribe during pregnancy. What does the rheumatologist need in order to provide answers to his patients? Where can the woman find (more) answers to her questions? How can researchers help the rheumatologists as well as the patient to fulfill the needs they have? It becomes clear that the treatment of young women who are pregnant or desire to become pregnant is rather complex as a variety of factors must be taken into account. Each of the latter should be investigated and discussed from the point of view of the patient, rheumatologist and researcher.

Box 1. Factors involved: an example

A woman indicates to her rheumatologist that she wants to become pregnant and wonders if she should stop her drugs. The woman is using methotrexate, etanercept, prednisone and naproxen on demand. With advice from the rheumatologist she stops both DMARDs and continues with the other drugs, after 6 months she will start trying to conceive. However, due to increased disease activity after a few months the use of DMARDs has to be reconsidered. The patient wishes she had known about this possibility of increased disease activity, this would have prepared her better, she said. In concordance with the rheumatologist she starts using etanercept again and then, unexpectedly, she becomes pregnant. She is really worried about the consequences of the use of etanercept for her unborn child. She looks for information to reassure her but the Internet shows different things and she does not know what to believe and what not. On some Internet sites she finds women who ended their pregnancy, but others say healthy children are born after the use of etanercept. She does not know what to do and discusses this with her rheumatologist. It is recommended not to use etanercept during pregnancy, confirms the rheumatologist, but there are also no indications that this drug poses a big teratogenic risk. Inofficially, it is even said that this drug can be used up to conception. The rheumatologist sais that is all he knows, at the moment no more information is available. She finds some reassurance in this answer, although she is still worried.

Drug utilization and safety studies

Drug utilization studies are a first step towards assessing the safety of a drug. When it is known if drugs are being prescribed to pregnant women, the magnitude of the problem can be determined.

Drug utilization: NSAIDs

Women with a rheumatic disease are often prescribed DMARDs in combination with NSAIDs (Non steroidal anti-inflammatory drugs). In a 2005 warning, it was stated by the Dutch registration authorities and others that NSAIDs and ASA (acetylsalicylic acid) should not be prescribed during the first trimester of

pregnancy unless this was strictly indicated, as might be the case in severe rheumatic diseases [1-3].This thesis shows that nevertheless 2.9% of the women were prescribed a NSAID or ASA during the first trimester (chapter 2). Over the counter NSAIDs were not taken into account in the IADB.nl (Interaction Database), so it can be assumed that even more women are exposed to a NSAID, especially in the first trimester when pregnancy might still be unknown. On the other hand, since a standardized gestational period was used, an overestimation of actual use is also to be expected. Either way, NSAIDs and ASA were prescribed in the first trimester of pregnancy and the question that remains is: 'Should physicians prescribing these drugs be *more* careful or are they careful enough?' To draw conclusions from the effect of the warning issued in 2005, data from 2005 onwards should show if prescribing has changed since then. Preliminary data show a slight decrease in the proportion of prescriptions, although not significant. To investigate whether these drugs are being prescribed according to guidelines, indications regarding NSAIDs are being prescribed are of added value. Since diagnoses are not available in the IADB.nl, a database such as the GPRD (general practice research database) might be helpful [4]. However, physicians who prescribe these drugs, should always be careful prescribing these drugs to women in the fertile age, especially when they suspect pregnancy is an issue.

Drug utilization: DMARDs

Chapter 3 showed that in the Netherlands approximately three per 1000 women (CI 95% 0.20-0.40) were prescribed a DMARD before pregnancy, and during pregnancy this was one per 1000 (13/12177; CI 95% 0.06-0.18). The results from this study indicate that prescribing of these drugs before and during pregnancy was based on the individual situation of the patient since patterns of prescribing were not found. In the United Kingdom (UK) one per 1000 women (CI 95% 0.12-0.14) was prescribed a DMARD before pregnancy as well as during pregnancy (CI 95% 0.13-0.15), as was shown in chapter 4 of this thesis. The decrease in prescribing of DMARDs round pregnancy will be partly due to guidelines being followed. Also the uncertainty of continuation or discontinuation of the DMARDs during pregnancy might have an influence.

In the Netherlands teratogenic drugs, such as methotrexate and leflunomide, were not prescribed before and during pregnancy in contrast to the UK. In both countries sulfasalazine and azathioprine were continued during pregnancy which is in concordance with recommendations. Hydroxychloroquine and chloroquine are hardly prescribed during pregnancy in the Netherlands in contrast to the UK where more then 100 women received a prescription for these drugs.

Explaining the differences: general issues discussed

The IADB.nl contains pharmacy dispensing data, so the prescriptions were prescribed by physicians (GP or specialist) and dispensed to the patient [5]. The GPRD contains data from the general practitioner (GP), and records only drug prescribed by the GP [4]. Drugs prescribed by the specialist will be registered as 'letter from the specialist' (or a comparable record) and a prescription will not be detected as such. In addition, the UK uses a traffic light system for prescribing drugs [6]. This system distinguishes between drugs prescribed by the GP only (green), prescribed by the specialist as well as the GP (shared care, amber) and drugs prescribed by the specialist only (red). Some DMARDs, TNFα-drugs are red, some others, azathioprine, sulfasalazine, are labeled amber. Amber means that the drug is initiated by the specialist and can be prescribed by the GP further on in the treatment. The combination of these factors might explain the difference found between the Netherlands and the UK. For both databases used in these utilization studies, it has to be noted that they do not reflect actual use of the DMARDs. This limitation can be handled by taking into account the continuity of prescribing. It can be assumed that DMARDs are being prescribed and dispensed on a regular basis. To calculate not only the number of prescriptions, but also the time for which the drugs is being prescribed, assumptions on continued use can be made. If drugs are being prescribed continuously, it can be assumed that these drugs are being taken. Olesen et al [7] showed that drugs used for chronic conditions were reported to be used always.

Cultural difference may also contribute to a difference in the use of drugs during pregnancy. In France it was estimated that 99% of the women received a

prescription for at least one drug during pregnancy (including vitamins).[8] In Norway drug prescription during pregnancy was estimated at 85%[9], in the US, 64% of the women were dispensed a drug (or medical supply) during pregnancy.[10] In the UK, it was estimated that approximately 65% of the women received a prescription for a drug during pregnancy[11], in the Netherlands, 79% of the women were prescribed a drug during pregnancy.[12] From these studies it appears that there are small differences between the UK and the Netherlands in prescribing drugs during pregnancy.

The prevalence of rheumatic diseases in the UK and the Netherlands are comparable [13;14] and guidelines towards drug use in rheumatic diseases are in principle the same [15-21]. It is therefore not to be expected that these factors contribute to the difference determined between the UK and the Netherlands.

Explaining the differences: individual DMARDs discussed

In the Netherlands, 8-24% of the pregnancies are unplanned [22], in the UK this is estimated at approximately 33% [23]. This higher number of unplanned pregnancies in the UK might contribute to the use of methotrexate and leflunomide in the first trimester of pregnancy. In the Netherlands, women who received one prescription of hydroxychloroquine or chloroquine and no other DMARD were excluded because it was assumed that these drugs were prescribed for malaria prophylaxis. In the UK these women were not excluded, which makes it difficult to compare the use of hydroxychloroquine and chloroquine. However, the number of women receiving hydroxychloroquine or chloroquine for another indication as malaria, is still much higher in the UK as seen in the Netherlands.

It should be discussed if the prescribing of DMARDs in both countries has to be improved and whether strict guidelines will help doing this. In addition, it should be investigated why the prescription of these drugs such as methotrexate and leflunomide was continued in the UK, and if guidelines with respect to these drugs need to be changed or other measures should be taken.

Drug safety: DMARDs

Since DMARDs are being used in daily practice, risk assessment studies can be performed to assess safety. To investigate the use of drugs in relation to birth defects, data need to be as detailed as possible. Meijer et al [24] described the importance of studying possible associations between drug use and birth defects at the most detailed level. They showed that the use of clomiphene was not associated with hypospadias in general, but a significantly increased Odds ratio was found for a severe form of hypospadias. This particular study was performed with data of EUROCAT Northern Netherlands (NNL), which records detailed information on birth defects as well as drugs prescribed and drugs actually used [25]. The GPRD is one of the largest databases used in pharmacoepidemiology research [4;26], but is not as detailed as the EUROCAT NNL or EUROCAT Central [27] with respect to the registration of birth defects. However, data from the GPRD can be used to detect a possible signal on the use of drugs in association with a certain birth defect. Using the GPRD (chapter 5), associations between azathioprine in the second trimester and prematurity was found (OR 3.25 (1.82,5.78)). This effect has been described before [28;29] and it has to be discussed if and how these findings should be translated into guidelines on the use of azathioprine during pregnancy. With respect to birth defects no associations were found. If a significant association would be found this could be regarded as a signal and this should be further investigated in databases such as EUROCAT NNL, EUROCAT Central [25] or Slone Epidemiology Center Birth Defects Study [30].

Rheumatologists perspectives and needs

Rheumatologists are the main health care providers for patients with a rheumatic disease. Rheumatologists are often confronted with a lack of evidence on the use of anti-rheumatic drugs during pregnancy (chapter 1 & 6)

Evidence on DMARD use in pregnancy

There is usually some time difference between approval of a drug to the market and the first reports on teratogenic effects. Methotrexate, nowadays recognized as a teratogenic drug, was approved for the market in 1953 (FDA), reports on

teratogenic effects were first published in 1960's [17]. Sulfasalazine was approved to the international market in 1944, case reports on teratogenic effects were published in 1980's [17]. Sulfasalazine is nowadays considered to be safe. Chapter 1 showed that most studies reporting on risks of DMARD exposure during pregnancy are based on case-reports or small exposed cohorts. A single case-report or small exposed cohort can, on its own, not be used to identify teratogenic effects. However, a combination of all case-reports and exposed cohorts might yield a signal which should lead to a detailed investigation. Case-control surveillances and follow-up studies are the most appropriate observational studies to detect moderate or high risk teratogens respectively. Follow-up studies only need limited numbers to identify a high teratogen drug, however, to identify moderate teratogens larger numbers are needed.[31] Norgard et al.[32] evaluated the teratogenic risk of sulfasalazine using in a case-control study, after signals became clear from case-reports and small exposed cohorts without an external control group. This, however, is an exception, in chapter 1 only two case-control studies [32;33] on the use of sulfasalazine during pregnancy and 1 large cohort on the use of azathioprine during pregnancy [34], were found.

Guidelines

It is reported by the rheumatologists that there is not a major need for supplementary guidelines. They are well aware of current recommondations and the lack of evidence with respect to the use of DMARDs during pregnancy, and they inform their patients accordingly. Guidelines are developed using current evidence, knowledge and experience of clinicians, giving physicians a tool to help treat their patients. There is always some time lag between the development of the guideline and its implementation in daily practice, and in rare situations this time lag may be considerable. The situation of women with a rheumatic disease and a desire to become pregnant does not occur very often and the benefit of guidelines needs to be wondered. It would be prudent, in the case of women with a rheumatic disease, to think a rigid guideline would be appropriate, the development of a dynamic guideline would be more appropriate. The development of this guideline should be initiated by the rheumatologists, but also other health care providers like

obstetricians and clinical pharmacists should be involved. The GPs, who have a more regular contact with there patients, pharmacists, who are experts when it comes to drugs, gynecologists, who might be involved in the treatment of complicated cases of rheumatic patients, should all be involved. The dynamic guidelines should focus on DMARD use, but also the use of NSAIDs and corticosteroids [16;18;20] should be taken into account. Organizations as the CBO (Centraal Begeleidings Orgaan) or the NVR (Nederlandse Vereniging van Reumatologie) could regulate this process. The panel of experts should generate a list of recommendations on each specific drug, where most common situations and exceptions should be addressed as well. These guidelines should be updated on a regular basis; e.g. once every two years, but they should also be updated when new information on these drugs become available such as safety updates. The recommendations can also be used by other physicians prescribing these drugs for other indications, although the effects of the indications should be reckoned with. Updates by means of courses or news letters might also be used to regularly inform rheumatologists on how to treat a woman with a rheumatic disease wishing to become pregnant.

Patients perspective

Chapter 7 of this thesis showed that women with a rheumatic disease had many questions about the use of their drugs and pregnancy. Most questions were about the use of drugs before or during pregnancy and fortunately most women received a satisfying answer to their questions.

Information sources

Information on the use of drugs in rheumatic diseases during pregnancy can be obtained at many different places, with the rheumatologist as the main source of information (chapter 7).

In a rheumatic disease, drugs are being dispensed in a regular manner and the pharmacy should be able to provide information on drug use during pregnancy. However, pharmacists are hardly consulted on drug use and pregnancy. If patients

are not aware that they can obtain their information in a pharmacy, they will not pose their questions there.

The Internet was mentioned as a source of information as well. Using the Internet you basically can find whatever you need, however, for many people it is difficult to distinguish between information that is true and useful and information that is not. Sources behind a website are often unknown or hard to identify. It is essential for the patient to know which of the information that was obtained provides the answers he/she needs. Websites from the National Association of Rheumatic Patients (Reuma Patienten Bond) and Dutch league against Rheumatism are helpful. They provide information leaflets, and links to other websites. In the northern and eastern Netherlands, some hospitals have information leaflets on the use of rheumatic drugs during pregnancy. However, a specific leaflet on the use of rheumatic drugs that contains information on DMARDs, NSAIDs as well as corticosteroids that is available to the general public, does not exist.

Questions and information

Women with a rheumatic disease had a lot of questions on drug use and pregnancy (chapter 7). Fortunately most questions were answered, but also a lot of questions will remain. It is impossible to answer all the questions, since not all the answers are known. Women with a rheumatic disease were mainly concerned on the use of their drug before and during pregnancy, less about the relapse of the disease after pregnancy and about drug use when breastfeeding. The majority of the responders in this study wanted to become pregnant at the time of the questionnaire. This might explain why a smaller proportion of the women had questions on the issues after pregnancy. It is, however, important to know what kind of questions women have on the use of their drugs during pregnancy, in order to be able to provide the answers needed. It seems that especially questions on drug use before and during pregnancy concern women, so it would be helpful to address these kinds of questions for example by developing a specific information leaflet.

The available information was found insufficient by the majority of the women, and many women reported no change or an increase in their doubts and fears about drug use and pregnancy. For those who expierenced an increase, it was difficult to determine what caused the increase of doubts and fears, but the lack of evidence plays a major role. When using sulfasalazine, answers might be more clear, since there is more information available on the use of this drug during pregnancy. TNFα-drugs and other biological are just recently approved for the market. Experience in general, but also of the individual rheumatologist is small, which makes it difficult to provide answers. Situations where rheumatologists might express their own fears and doubts about the use of a TNFα-drug but still recommend continuing the drug might occur. All risks and benefits have to be considered, including patient's disease and wishes. This might result in continuation of TNFα in one case and discontinuation in an other case.

Final remarks

This thesis explores, in particular, the safe use of DMARDs among female pregnant patients. It was shown that in the Netherlands DMARDs were prescribed on an individual basis. In the Netherlands guidelines with respect to methotrexate were followed, in contrast with the prescribing of methotrexate in the UK, which was continued during pregnancy. The use of both sulfasalazine and azathioprine was continued during pregnancy in the UK and the Netherlands, which is in concordance with recommendations. The use of azathioprine was associated with preterm birth, and it should be discussed whether recommendations with respect to the use of azathioprine in pregnancy should be changed. There is a lack of evidence with respect to the use of DMARDs during pregnancy which was acknowledged both by the women using these drugs as well as rheumatologists prescribing these drugs. Development of a dynamic guideline should be considered to support the rheumatologists. To keep the rheumatolgosts better informed, these guidelines should be updated more often then it is the case with rigid guidelines to keep the rheumatologists better updated. A special information leaflet on DMARDs and pregnancy would be considered of added value for women using these drugs.

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Prescribing of NSAIDs and ASA during pregnancy; do we need to be more careful? Br J Clin Pharmacol. 2008 Feb;65(2):275-6.[abstract]

Samenvatting

Vroeger werden vrouwen met een reumatische aandoening afgeraden kinderen te krijgen. De toenmalige behandeling van reumatische aandoeningen concentreerde zich met name op pijnstilling. Tegenwoordig wordt er vooral gebruik gemaakt van DMARDs (disease modifying anti-rheumatic drugs). Methotrexaat is in de huidige richtlijnen een eerste keus geneesmiddel maar er worden ook vaak combinaties van verschillende DMARDs toegepast. Recent ontwikkelde geneesmiddelen, de 'biologicals' zoals TNFα-geneesmiddelen (Tumor Necrosis Factor), worden met name toegepast als de combinatie van DMARDs niet werkt. De kennis over de veiligheid van DMARD gebruik tijdens zwangerschap is zeer beperkt. Classificatie systemen proberen een indicatie te geven over de veiligheid van het geneesmiddel tijdens zwangerschap. Methotrexaat en leflunomide worden ontraden evenals de nieuwe TNFα's. Bij andere geneesmiddelen zoals azathioprine moeten de voor en nadelen worden afgewogen, sulfasalazine lijkt als enig geneesmiddel veilig gebruikt te kunnen worden in de zwangerschap.

Tijdens de behandeling van reumatische aandoeningen bij jonge vrouwen met een zwangerschapswens zullen afwegingen gemaakt moeten worden. Vrouwen zelf zullen vragen hebben over het geneesmiddelen gebruik tijdens de zwangerschap, maar ook over de relatie tussen de aandoening en haar kind. Reumatologen zullen proberen deze vragen te beantwoorden met behulp van de beschikbare informatie. Maar ook het internet zal veelvuldig geraadpleegd worden als informatie bron en mogelijk tegenstrijdige informatie geven. Het zal voor de patiënt soms moeilijk zijn een goed oordeel te vormen.

In hoofdstuk 1 wordt een overzicht van de beschikbare literatuur over DMARDs en zwangerschap gepresenteerd. Dit overzicht onderstreept het ontbreken van data aangaande de veiligheid en risico's van DMARD gebruik tijdens de zwangerschap. Wij vonden observationele studies: twee case controle studies en één grote cohort. Daarnaast zijn er kleine blootgestelde cohorten en individuele gevallen beschreven. De gevonden studies laten zien dat methotrexaat in de zwangerschap niet gebruikt moet worden, de risico's van het gebruik wegen duidelijk op tegen de mogelijke voordelen van de behandeling. Gebruik van azathioprine tijdens de

zwangerschap kan overwogen worden. Er zijn indicaties voor foetale risico's maar toch kunnen de voordelen van het gebruik van azathioprine opwegen tegen de mogelijke risico's. Sulfasalazine lijkt veilig gebruikt te kunnen worden in de zwangerschap. Met betrekking tot hydroxychloroquine laten de gevonden resultaten zien dat hydroxychloroquine in lage doseringen veilig gebruikt zou kunnen worden bij SLE (systemische lupus erythematodes) en RA (Reumatoïde artritis). Hierbij moet echter opgemerkt worden dat deze conclusies zijn gebaseerd op kleine blootgestelde cohorten. Voor andere DMARDs, zoals leflunomide, goud preparaten en TNFα's, is de beschikbare informatie nog beperkter. Alleen kleine blootgestelde cohorten of beschrijvingen van individuele gevallen zijn beschikbaar. Case beschrijvingen en case series zijn vaak de eerste signalen voor de klinische praktijk over een mogelijke afwijkende zwangerschapsuitkomst na gebruik van een geneesmiddel. Echter, deze case beschrijvingen en series worden bijna nooit gevolgd door analytische studies zoals case controle surveillance of follow-up studies, zoals uit het literatuur overzicht naar voren komt. Er is meer tijd nodig om genoeg data te verzamelen zodat er een degelijke case controle studie of een grote cohort studie kan worden uitgevoerd.

In hoofdstuk 2, 3 en 4 wordt het gebruik van DMARDs en andere antireumatische geneesmiddelen, NSAIDs (non-steroidal anti-inflammatory drugs) voor en tijdens de zwangerschap beschreven. Immers, de veiligheid van deze geneesmiddelen tijdens de zwangerschap is helemaal niet aan de orde als deze geneesmiddelen niet worden gebruikt in de zwangerschap. De uitgevoerde studies bevestigen dat zowel DMARD's als NSAIDs tijdens de zwangerschap gebruikt worden. In 2005 kwam de EMEA (European Medicines Agency) met een waarschuwing over het gebruik van NSAID's in het eerste trimester van de zwangerschap. Uit recente studies kwamen associaties met NSAIDs gebruik en verschillende aangeboren afwijkingen naar voren. Er werd daarom aangeraden om NSAIDs niet te gebruiken in het eerste trimester van de zwangerschap tenzij dit stikt noodzakelijk was. Om te zien of deze geneesmiddelen in Nederland in de zwangerschap werden voorgeschreven, is er een database studie uitgevoerd met de IADB.nl, waarin apotheekgegevens zijn opgenomen. Uit deze studie bleek dat in 3.9% van de

zwangerschappen een NSAIDs (of acetylsalicyl zuur) werd voor geschreven. In 2.9% van de zwangerschappen werden de geneesmiddelen voorgeschreven in het eerste trimester. Omdat vrij verkrijgbare pijnstillende geneesmiddelen niet zijn meegenomen in deze studie, is de verwachting dat het werkelijke aantal gebruikers hoger ligt. De resultaten geven een overzicht van de voorgeschreven NSAIDs tijdens de zwangerschap voor de waarschuwing van EMEA. Toekomstig onderzoek zal moeten uitwijzen of het gebruik na de waarschuwing is afgenomen..
Hoofdstuk 3 beschrijft het gebruik van sulfasalazine, azathioprine en methotrexaat in de IADB.nl rondom de zwangerschap. Vijfendertig vrouwen ontvingen een recept voor één van deze geneesmiddelen voor hun eerste zwangerschap. Geen van deze vrouwen gebruikte methotrexaat tijdens de zwangerschap, dat is in lijn met de richtlijnen. Van de vrouwen die voor hun zwangerschap azathioprine gebruikten, gebruikte 60% het geneesmiddel door tijdens de zwangerschap. Voor sulfasalazine lag dit op 38%. Vrouwen die sulfasalazine als initiële DMARD ontvingen, gebruikte daarnaast ook anti-inflammatoire en antireumatische geneesmiddelen. Voor de vrouwen die azathioprine als hun initiële geneesmiddel ontvangen waren dat corticosteroïden en intestinale anti-inflammatoire geneesmiddelen. Er werden geen specifieke patronen gevonden in het gebruik van DMARDs voor en tijdens de zwangerschap. Gebaseerd op deze resultaten kan geconcludeerd worden dat DMARDs en gerelateerde co-medicatie voorgeschreven worden op basis van de karakteristieken van de individuele patiënt.
In hoofdstuk 4 wordt het gebruik van DMARDs voor en tijdens de zwangerschap onderzocht met behulp van data uit de General Practice Research database (GPRD). De DMARDs werden het meest voorgeschreven voor malaria profylaxe (chloroquine), maar ook andere DMARDs zoals azathioprine, hydroxychloroquine en sulfasalazine werden regelmatig voorgeschreven. Methotrexaat en leflunomide werden minder vaak voorgeschreven. De meerderheid van de vrouwen die azathioprine en sulfasalazine kregen voorgeschreven in de 3 maanden voorafgaande aan hun zwangerschap, kregen deze geneesmiddelen ook tijdens de zwangerschap. De andere geneesmiddelen werden meestal gestopt in het eerste trimester van de zwangerschap. Methotrexaat werd in sommige gevallen

tijdens de zwangerschap gebruikt, wat niet in overeenstemming is met de nationale richtlijnen. Mogelijke redenen voor het niet stoppen van methotrexaat kunnen niet worden achterhaald via deze database, maar het is mogelijk dat het niet plannen van de zwangerschap een rol speelt. In het algemeen nam het gebruik van DMARDs voor en in de zwangerschap af. Dit kan deels worden toegeschreven aan het volgen van de richtlijnen, maar het is ook mogelijk dat de onzekerheid betreffende veiligheid van DMARDs in de zwangerschap een rol speelt. Voor de meeste geneesmiddelen nam de hoeveelheid en duur van het gebruik in het tweede trimester toe ten opzichte van het eerste trimester.

De verschillen in het gebruik van DMARDs in de zwangerschap tussen Nederland en de UK kunnen verklaard worden door culturele verschillen maar ook het gebruik van een andere database kan de reden zijn. De gedetailleerde informatie, beschreven in voorgaande studie, kan gebruikt worden om eventuele relaties tussen de blootstelling aan DMARDs en bepaalde aangeboren afwijkingen, te evalueren. Resultaten laten zien dat er geen verhoogde risico's zijn waargenomen tussen het gebruik van DMARDs in het eerste trimster en aangeboren afwijkingen of zwangerschapsterminatie (hoofdstuk 5). Wel werd er een verhoogd risico gezien op vroeggeboorte en het gebruik van azathioprine in het tweede trimester vergeleken met vrouwen die geen DMARD hebben gebruikt. In eerdere studies werd de associatie tussen azathioprine gebruik en vroeggeboorte reeds beschreven, alhoewel er grotere studies nodig zijn om de associatie te bevestigen. De resultaten lieten ook een niet significant verhoogd relatief risico zien tussen vroeggeboorte en blootstelling aan hydroxychloroquine in het 2de en 3de trimester. Hydroxychloroquine wordt meestal voorgeschreven bij SLE en SLE is in verschillende studies geassocieerd met vroeggeboorte. Of de onderliggende ziekte (SLE) een confounding factor is of dat het geneesmiddel geassocieerd is met het verhoogde risico, kan op basis van deze gegevens niet worden vastgesteld. Dit onderzoek is uitgevoerd met als doel hypothesis te genereren over aangeboren afwijkingen en DMARD gebruik. Bij het onderzoeken van associaties tussen bepaalde aangeboren afwijkingen en het gebruik van een geneesmiddel, is het nodig gebruik te maken van gedetailleerde data. De data met betrekking tot

geneesmiddelen gebruik in de GPRD is van goede kwaliteit, echter data met betrekking tot aangeboren afwijkingen is minder gedetailleerd vastgelegd.

Naast inzicht over het gebruik en de veiligheid van DMARDs tijdens de zwangerschap, is het ook belangrijk inzicht te hebben in de huidige klinische praktijk. Bijvoorbeeld om te zien of de behandeling of voorlichting aangepast moet worden. Interviews met reumatologen (hoofdstuk 6) laat zien dat ondanks het feit dat het bewijs met betrekking tot de veiligheid van DMARDs tijdens de zwangerschap zeldzaam is, er geen grote behoefte bestond aan additionele richtlijnen. Het gebrek aan bewijs is enigszins voor de hand liggend en kwam ook naar voren in het literatuur overzicht (hoofdstuk 1). Volgens de reumatologen zijn de richtlijnen met betrekking tot het gebruik van sulfasalazine, methotrexaat en leflunomide tijdens de zwangerschap duidelijk. Sulfasalazine kan in de zwangerschap doorgebruikt worden, de laatste twee geneesmiddelen moeten voor de conceptie gestopt worden. De respondenten gaven ook aan dat geneesmiddelen zoals azathioprine, cyclosporine en hydroxychloroquine gebruikt kunnen worden als dat nodig is maar dit moet zorgvuldig worden overwogen. Methotrexaat en sulfasalazine zijn eerste keus geneesmiddelen in de algemene behandeling van RA. Echter, als een vrouw zwanger is of wil worden dan geeft men de voorkeur aan sulfasalazine of het geheel stoppen van de geneesmiddelen. De ervaring die reumatologen hebben met zwangerschap bij reumatische patiënten is beperkt, de reumatologen geven aan dat ze maximaal 20 zwangere patiënten per jaar zien. Daarom geven de meeste reumatologen hun patiënten een op maat gemaakt advies, gebaseerd op de karakteristieken van de patiënt. Men gaf aan dat een additionele richtlijn waarschijnlijk niet zou leiden tot een beter advies. In het algemeen zijn de Nederlandse reumatologen van mening dat er voldoende informatie is om vrouwen met een reumatische aandoening en een zwangerschap of zwangerschapswens te behandelen.

In het laatste hoofdstuk worden de ervaring van vrouwen beschreven; welke vragen hebben zij over DMARD gebruik bij een zwangerschapswens. Door middel van een schriftelijke vragenlijst is bij vrouwen met een reumatische aandoening (n=50) onderzocht welke vragen zij met name hadden en of zij antwoorden hebben gevonden op deze vragen. De meeste vrouwen, die deelnamen aan dit onderzoek

waren gediagnosticeerd met RA en de ziekte van Bechterew. De resultaten laten zien dat het gebruik van methotrexaat en TNFα afnam zodra vrouwen bewust bezig waren met hun zwangerschapswens, het gebruik van sulfasalazine nam toe. Ongeveer tweederde van de respondenten gaf aan dat hun vragen naar tevredenheid werden beantwoord. De vrouwen hadden met name vragen over geneesmiddelen gebruik voor en tijdens de zwangerschap en over de schadelijkheid van het geneesmiddel voor hun ongeboren kind. De vrouwen gaven aan dat ze hun vragen vooral stelde aan de reumatologen of gebruik maakte van de media (inclusief internet). Ongeveer 40% oordeelde dat de beschikbare informatie voldoende was, een grote meerderheid gaf aan dat een specifieke brochure over zwangerschap en geneesmiddelen gebruik van toegevoegde waarde zou zijn. Gevoelens van twijfel en angst bleven bestaan of namen toe na het bekijken van de beschikbare informatie voor het grootste deel van de vrouwen.

Het gebruik van DMARDs tijdens de zwangerschap werd in dit proefschrift onderzocht. Uit de literatuur kwam naar voren dat gegevens met betrekking tot de veiligheid van DMARDs tijdens de zwangerschap ontbrak. Dit werd door zowel de reumatologen als de patiënten onderstreept. Patiënten gaven dan ook aan dat een brochure over geneesmiddelen en zwangerschap van toegevoegde waarde zou zijn. Reumatologen daarentegen gaven aan dat zij geen behoefte hadden aan additionele richtlijnen. DMARDs worden zowel voor als tijdens de zwangerschap gebruikt, er is echter geen specifiek patroon in het gebuik waar te nemen. Patiënten ontvangen een op maat gemaakt advies met betrekking tot geneesmiddelen gebruik in de zwangerschap, die voldoet aan de individuele karakteristieken van de patiënt. Ditzelfde werd ook aangegeven door reumatologen. Het gebruik van DMARDs werd niet geassocieerd met een toename van specifieke aangeboren afwijkingen. Wel was er een toename van vroeggeboorte waar te nemen na gebruik van azathioprine in het 2de trimester. Deze bevindingen zullen echter in grotere studies bevestigd moeten worden.

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Curriculum Vitae

Fokaline Vroom was born in Bant (Noordoostpolder) on January 22, 1977. In 1995 she started studying Nutrition and dietetics in Groningen where she received her Bachelors in 1999. In 1999 she continued here studying with Pharmacy where she received her Masters in pharmacoepidemiology in 2004. Her master thesis about orofacial clefts and lifestyle factors was written in Nijmegen (department of epidemiology and biostatistics). In an additional project the use of oral contraceptive in the Netherlands was studied. During her studies she was appointed as an teaching assistant several times to introduce first year students in the world of social pharmacy.

In 2004, Fokaline was appointed as a PhD student at the department of Social Pharmacy, Pharamcoepidemiology and Pharmacotherpay at the Univeristy of Groningen on the project pregnancy and DMARDs. As part of her PhD project, Fokaline visited the Pharmacoepidemiolgy department of the University of Surrey, Guildford, UK, between June 2007 and October 2007 to study the use of DMARDs as well as the safety of DMARDs during pregnancy using the GPRD. This all resulted in her theis entitled “Drug use in pregnancy. Exploring the field of disease modifying anirheuamtic drugs in pregnancy“ which she will defend on March 20, 2009. Since June 2008, Fokaline has been working as a pharmaceutical assessor/researcher at the centre for the Quality of Chemical-Pharmaceutical Products at the RIVM in Bilthoven.

Fokaline is a member of the Royal Dutch Pharmacetical Sociaety (KNMP), the Neterhalnds Epidemiology Society (VvE), the Dutch association for Rheumatology (NVR) and the Intrnational Society for Pharmacoepidemiology (ISPE).

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